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IRITIS BOECK (SARKOID OF BOECK IN IRIS)

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WHEN Caesar Boeck described the benign dermal sarkoid in 1899, he advanced the supposition that the same disease might affect other tissues besides the skin. That he was right in his surmise has been confirmed by a great number of publications; the material has recently been reviewed historically by Waldenström.[42] The conception: "Boeck's sarkoid" has been extended very much. I use the term Boeck's disease because it prejudges nothing as to the nature of the disease, and because the most proper denomination of the disease is still a matter of debate.

Boeck, then, gave a description of a skin disease; in 1914 Schaumann showed that the same affection, with or without dermal symptoms, may occur in the whole system of lymphatic tissue including the tonsils, as also in the marrow of bones, lungs, spleen and liver. He therefore took it to be a systemic disturbance of the lymphatic tissue and named it "lymphogranulomatosis benigna."

In 1933 Pautrier and Oberling set up the hypothesis that the affection might be a systemic disease of the reticulo-endothelial tissue (dermatological congress in Strasbourg). Fresh reports of

Boeck's disease being localised outside the lymphatic tissue are constantly appearing, and such points of resemblance have been pointed out between Boeck's disease and a series of other pathological pictures, most recently Heerfordt's uveoparotid fever, that perhaps it should be classed among a larger group of diseases. Even now the conception of a systemic disease can only be kept up by the supplementary hypothesis that some system is affected primarily and a secondary haematogenous dissemination to other organs follows. There is an increasing tendency to look upon Boeck's disease as a universal disturbance which affects all the organic systems (Waldenström[42]). Thus the proportion (or disproportion) of the diffusion through the organism to its clinical manifestations becomes one of the most striking features of this peculiar affection.

Clinically Boeck's disease is characterised by following a more or less symptomless, torpid course, with a progressive tendency and spontaneous remissions and generally a favourable prognosis. Its *histological* picture is uniform all through the organism, and therefore is a chief diagnostic point: In the affected tissue there are found heaps of epithelioid cells surrounded by a sparse hedging of lymphocytes; in the midst of the epithelioid cells a few giant cells of the Langhans' type are found, but no hyaline degeneration, necrosis or sclerosis. These are the chief histological features. The epithelioid groups of cells are often, especially in the skin, placed quite close to minor vessels (Kissmeyer[17]); according to Pautrier and Oberling[25-26] they often contain reticulocytes, which is the basis for the theory of Boeck's sarkoid being a reticulo-endothelial systemic disease. Wahlgren[41] observes that sometimes there appear Langhans' giant cells which contain round or oval calcifications, and that "there has been an attempt to ascribe to them a certain diagnostic import."

Finally *the relations between Boeck's disease and tuberculosis* are of the greatest diagnostic and clinical importance, though as yet they remain theoretically uneludicated and are interpreted in widely different ways. In strikingly frequent cases patients with Boeck's disease belong to non-tuberculous families and are personally unaffected with clinical tuberculosis (Nordin[24]). Tubercle bacilli have never been unquestionably demonstrable in Boeck's sarkoid, and inoculation of guinea-pigs does not take effect. Furthermore, it has been established beyond question by different authors (Schaumann, Bonnevie and With) that patients with clinical manifestations of Boeck's disease have *a negative or extremely feeble cutaneous tuberculin reaction.* These patients, however, seem to be taken with tuberculosis rather often; when this happens, the symptoms of Boeck's disease disappear, and the negative tuberculin reaction changes into becoming positive.

Whether Boeck patients have a special predisposition to tuberculosis is an open question. Sundelin[39] thinks that the patients are often exposed to contagion because—owing to the difficulty of diagnosis—they are often sent to tubercle-hospitals and sanatoria. In about half of the clinically established cases of Boeck's disease in which a post-mortem has been performed, the cause of death has been intercurrent tuberculosis in lungs, peritoneum or elsewhere.

In the literature four or five cases of Boeck's disease are reported (see Schaumann,[34] and Wahlgren[41]), in which the patients have died of this disease; in these cases the cause of death was cardiac debility. One case, described by Watz,[43] gives an impression of the prognosis of the uncomplicated Boeck's disease. In one case, in which there were large hilus shadows and the patient had difficulty in breathing, 605 grammes of glandules, coalescing with aorta, the capital veins and trachea, were removed by operation. The patient died 16 years after the operation of cardiac insufficiency; nodules the size of a clenched hand had then developed afresh in the mediastinum.

The sectional cases show that the specifically Boeckean alterations occur extensively in organs which during life did not even convey an impression of being affected, and form an interesting background to Schaumann's contention: that the tonsils and the lymphatic glandular system are invariably affected in Boeck's disease, symptoms or no symptoms.

Boeck's disease is found localised with particular frequency in certain organs. It is possible that these organs are attacked electively; it is also conceivable that they react through symptoms which are most likely to attract the patient's attention and make him seek medical advice (skin), or that the diagnostic faculties are specially effective in certain localities (bones, lungs).

I shall give a brief account of the most common manifestations of Boeck's disease.

The *dermic alterations* I think are prevalent. The start of the disease as a dermatological affection may have turned the attention to them preferentially. Most often they are localised in the face, shoulders, and extensor sides of the extremities. Three forms are distinguished: (1) a relatively rare, knotty form with nodules of from 1 mm. to the size of peas, yellow or red, which gradually turn bluish, their central portion at the same time caving in, while the edge keeps yellow. (2) "The nodular sarkoid"—the most frequent form: larger nodes, issuing from the deeper strata of the skin, indolent, hard, never ulcerous; reddish in colour, changing into brownish, dwindling by degrees, leaving a pigmentation with teleangiectatic edge. (3) "Lupus pernio"-form: doughy, bluish red, cutaneous or subcutaneous tumours without

sharply defined outlines. (4) Furthermore Schaumann has described a " forme érytrodermique," which is extremely rare, but theoretically interesting, its existence constituting a morphological accordance between the dermic symptoms in " lymphogranulomatosis benigna " (Boeck-Schaumann) and lymphogranulomatosis maligna (Hodgkin).

In the bones of the hand and foot not infrequently cystic rarefied areas are found (osteitis cystica Jüngling,[16] from Danish *hand especially studied by Jens Nielsen*[23]), which are demonstrable by Roentgen rays, but need not give any clinical symptoms at *all. In contrast with the tuberculous spina ventosa,* the osteitis cystica is said to give no periosteal reaction, and therefore less *thickening of the bone. It has been established pathologico-*anatomically that the marrow of the bones may be affected, though *this fact does not come out in Roentgenograms.*

Boeckean alterations in the lungs appear in skiagrams as *enlarged hilus-shadows, reticular or irradiating striation or woolly* spots. The apex of the lung is comparatively seldom affected, and caverns are not seen; the picture is not a specific one; it may remind one of tuberculosis, silicosis or stasis.

Descriptions have been given of Boeck's disease in the lacrymal and salivary glands, epididymis, mamma, in striated and cardiac muscles, in the mucous membrane of the lacrymal duct, the nose, the sheaths of peripheral nerves, and the hypophysis (Sundelin,[39] Waldenström,[42] Salvesen[29]). As regards the eye, Boeck's sarkoid has been described as occurring in the conjunctiva, cornea, iris, choroid and the optic nerve.

In the *conjunctiva* Boeck's disease takes a rather characteristic shape: it forms rows or groups of clear, hyaloid or yellowish nodules, which do not bother the patient noticeably, there is a moderate mucous discharge, the cornea is not invaded, and there is no swelling of the preauricular glands. The diagnosis is easy, because the nodules present the typical histological structure. (Strandberg, Lehrfeld, Schoeppe, Lütz, Igersheimer, Blegvad.)

The *corneal* affection is rare. Only in one case, Stumpke,[38] has keratitis been described as the only ophthalmic symptom: in a patient with Boeck's sarkoid as a dermal affection small superficial opacities of the cornea were found; in six other cases (Weidmann,[45] Favauge-Bruyel,[9] Plancherel,[27] Schoeppe,[35] Mylius,[21] Nordin[24]), the question is about parenchymatous processes which set in late in the course of the disease, together with nodular iritis. Plancherel and Schoeppe give strikingly uniform descriptions of a downward process in the cornea, deep, fusiform with down-turned basis.

Iritis in Boeck's disease has during latter years been brought to the front owing to the discussion of the relations between Boeck's disease and uveoparotid fever. When iritis is alleged

to be of quite common occurrence in Boeck's disease, this is probably drawn from Bloch, who in 1915 counted up 5 cases of iritis among 20 with Boeck's disease. In the Table on page 156 I have tabulated 27 cases of iritis in Boeck's disease, which is all I have been able to find among about 500 cases in the literature on this disease. The table, then, seems to me to show that iritis in Boeck's disease is rare, and that it may occur as part of a clinical picture which cannot be compared and far less identified with uveoparotid fever.

On one point all authors agree, however different their points of view; that clinically, iritis Boeck closely resembles tuberculous iritis. Schumacher and Bering, who made the first observations, did not doubt at all that the iritis must be tuberculous, Favauge-Bruyel even thought that the apparently tuberculous character of the iritis furnished a proof that Boeck's disease was a special form of tuberculosis. That a distinct form of iritis exists which must be characterised as Boeck's disease, has been proved histologically by Mylius and Schürmann.[22] The curious clinical points of contact between morbus Boeck and tuberculosis have been briefly mentioned above; the relations between the two diseases have been investigated experimentally and discussed theoretically by numerous researchers (Jadassohn, Martenstein, Kyrle, Schaümann, etc., etc.); an interesting contribution has recently been put in by Lemming.[19] How important the distinction between iritis Boeck and tuberculosis may be, and how difficult the differential diagnosis, is illustrated by the following case history:

The patient is a young girl, R. J., born April, 1921. No cases of tuberculosis in the family. A brother died of cerebro-spinal meningitis in connection with vaccination, the patient herself was very ill with meningeal symptoms when she herself was inoculated at 7 years of age, otherwise in perfect health.

On October 20th, 1935, she went to a practising ophthalmologist in Copenhagen. The right eye was found to be normal, V.6/6, emm. (unaltered all along), left eye, V.6/9, emm., slight kerato-iritis. Atropine was prescribed.

10th day of illness: A round nodule, size 1 mm., in the angle of the anterior chamber at "10 o'clock." Depth of chamber: normal. Ophthalmoscopy normal. The keratitis cured. Slight ciliary injection. No pain.

21st day: The nodule at "10 o'clock" grown into 2 mm. in diameter, 2 other nodules developing between "10 and 6 o'clock," ½-1 mm. in size. The nasal half of the chamber deeper. V.6/9.

37th day: Admitted to a hospital. State of nutrition: middling, weight 53·900 (height 168). Temperature: normal. No tiredness or perspiration. Sedimentation rate 7 mm. 1 hour, Mantoux ÷(0·1—1 mgr.), Wassermann Reaction ÷, hæmoglobin 82 per cent. (Sahli). No swelling of the jugular, salivary or lacrymal glands. Steth. card., natural. Steth. pulmon., slight dullness in left infraspinata, towards spine, but no bronchial breathing or râles. Abdomen: natural. Roentgenogram of the lungs: enlarged hilus-shadow, scattered woolly spots—described as mediastinitis with small peripheral infiltrations. Left eye: Cornea hypæsthetic, tension normal. Nodules round, not granulated, grey, nacreous, slightly vascularised, covered in part with exudates. Treatment, Finsen rays, avital injections.

67th day: Continuously apyretic, general health unaffected. Left eye, V.6/36 unimproved by glasses, cornea anæsthetic. The chamber ever deepening, 2 fresh

nodules developing in the angle and one in pupillary zone of the iris. No precipitates. Aqueous flare (measured a.m. Rönne) 2·00 that is, slightly increased.

158th day: Finsen ray treatment continued ambulatorily. The patient is fit for work (shop assistant, 8 hours daily), apyretic, without pulmonary symptoms. The affected eye causes the patient very little annoyance, the vision, however, has declined, V.: hand movements at 1 metre. The chamber infundibularly retracted. Numerous synechiae, the anterior surface of the lens covered with exudates. A few precipitates (Fig. 1a).

218th day; A nodule, situated at "8.30 o'clock," has encroached upon the sclera (Fig. 1b).

275th day: Wide ingrowth into sclera from 4 nodules (Fig. 1c).

349th day: Though the left eye is almost indolent, and the nodules do not increase further in number or size, the aspect keeps growing still more alarming, the sclera becoming thinner over the nodules and seeming to threaten perforation. The general health still continues good. The patient's family and the patient herself have been gradually reconciled to the thought that the eye is lost, and she is once more removed to a hospital expressly with a view to enucleation. Weight, 59·000. Temp., normal. Sedimentation rate 7 mm. an hour. Mantoux: ÷ 0·01—0·1—1mgr. Hgb. 69 per cent. (Haldane). Steth. pulmon., unchanged as when first admitted. Left eye, V.2/60. Cornea hypæsthetic, tension, normal. A few precipitates. Depth of chamber, 4 mm. The nodules described much as on the 37th day as regards appearance, spec. note: they do not show any sign of necrosis. At "7 and 9 o'clock" they bulge out the sclera very much, in these places it is very thin, almost pellucid (Figs. 1c and 2).

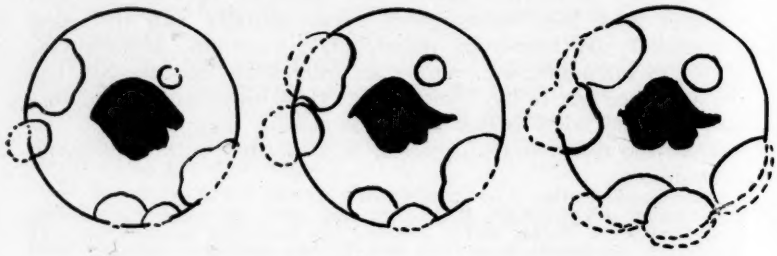
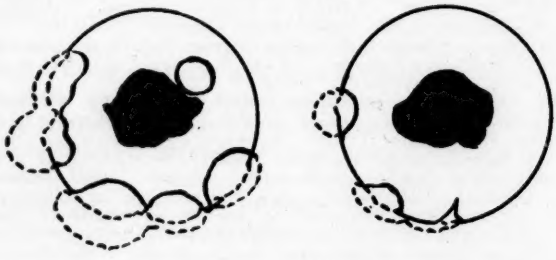


Fig.1 a 158 b 218 c 275



d 407 e 540

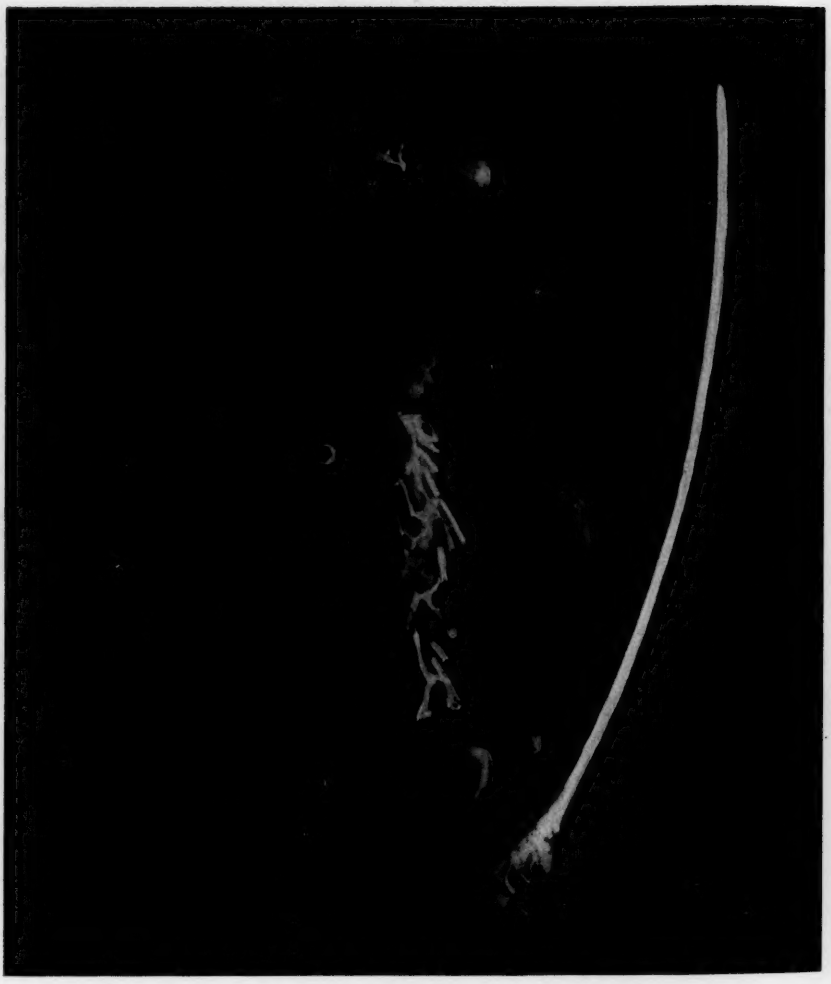


FIG. 2. (Drawing by the Author)

Slit-lamp appearance on 349th day. Cornea normal, aqueous flare normal. A few precipitates. Enormous nodules. Synechiae and thin coating of the anterior surface of the lens.

Ophthalmoscopy: impossible owing to exudate on the anterior surface of the lens.

X-ray of lungs: Besides an enlarged hilar shadow, both lungs packed with disseminated woolly flecks so closely that there is reason for suspecting miliary tuberculosis, possibly, but on the face of it with less probability, Boeck's sarkoid (Fig. 3a).

Therefore the patient was dismissed without operation. Before discharge she was examined with special regard to symptoms of Boeck's sarkoid. The skin, the lacrymal and salivary glands, as also all palpable lymphoid glands

FIG. 3a.

Roentgenogram of lungs, 349th day. Description: see text.

were normal, radiograms of the long tubular bones and the bones of the hands and feet revealed nothing abnormal.

407th day: Since leaving hospital she has been performing her usual work, without feeling any tiredness. The temperature has been normal (measured twice a day). No cough, no shortness of breath. Weight 62·000. Left eye, V.2/60. The ciliary injection is decreasing, *all of the nodules are absorbing*, at " 6 o'clock " a few fresh small granulations in the angle of the chamber (Fig. 1d).

534th day: Mantoux: ÷ 0·1—1 mgr.

540th day: Left eye: V.6/36 + 2·00 cyl. 120°. *The nodules have disappeared* with the exception of one at " 9 o'clock " in the angle of the chamber, in this place the sclera is bulging, but not cystic. Renewed general examination,

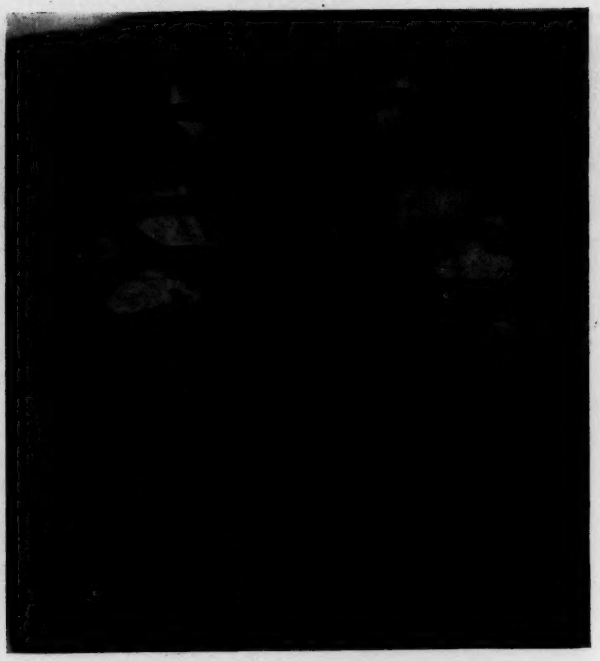


FIG. 3b.

Roentgenogram of lungs, 708th day.

medical and dermatological: nothing new. Radiogram; a considerable clearing of the peripheral patchy consolidations. The bones of the extremities keep normal.

640th day: General condition unaltered. Weight: 63·500. Left eye: V.6/18 + 2·0D. cyl. 120° ÷ 1·0D. sph. All the nodules disappeared. At " 6 o'clock " a whitish cicatrix in the angle of the chamber; the depth of the chamber keeps slightly increased. A few precipitates.

708th day: The temperature still ascertained at intervals, and it is always normal. Weight: 63·500. Left eye: V.6/12 + 2·0D. cyl. 120° ÷ 1·0D. sph. A few pigmented precipitates. Depth of chamber: 3·8 mm. In the angle of the chamber a small white cicatrix, at " 9 o'clock " a slight thickening of the sclera and an atrophic and pellucid spot in the iris. *Otherwise the stroma of the iris is normal* throughout, without cicatrices from nodules. The pupil is irregular as a consequence of numerous synechiae. A thin coating of the anterior surface of the lens. Ophthalmoscopy: The fundus is seen blurred, but is normal. Field of vision: normal. General examination, medical and dermatological: nothing abnormal. X-ray of lungs: Left hilus shadow still enlarged. Only in the lower portion of both lungs are found remnants of the consolidations and opacities mentioned above, the upper part of the lungs is now normal (Fig. 3b).

From the left tonsil (perfectly normal in appearance) a probatory excision was made, and sections showed Boeck's sarkoid. I quote at length a histological opinion given by the University Institute for pathological anatomy.

A histological examination of the submitted specimen from the tonsil shows the surface covered with naturally structured stratified epithelium. Under this the usual lymphoid stroma with germ centres is seen, and in places a slight increase of the collagenous connective tissue. In the outer layers which are situated nearest to the epithelium, the stroma is the seat of focal, productive, inflammatory processes with formation of rather closely packed, light heaps of cells, which show out in rather sharp contrast with the lymphoid surroundings. The borderline is not circular, as in germ centres, but scalloped or lobate. The dimensions of the foci in question are supposedly a little below the average size of germ centres. In shape and size the elements are like epithelioid cells, with rather large, but scantily chromatinized nuclei. In a few places plurinuclear formations are seen, one at least of which looks much like a Langhans' giant cell. In other places pre-capillary vessels are found which are continued all the way into the epithelioid heaps, and here there is a gradual transition between the adventitious vascular elements and the large light cells of the infiltrations. No signs of caseation are found at all, typical elementary tubercles have not been traced, nor any sign of syphilitic processes; no tumefaction observed. Histological diagnosis: alterations of tissue corresponding to what is found in the so-called Boeck's sarkoid.

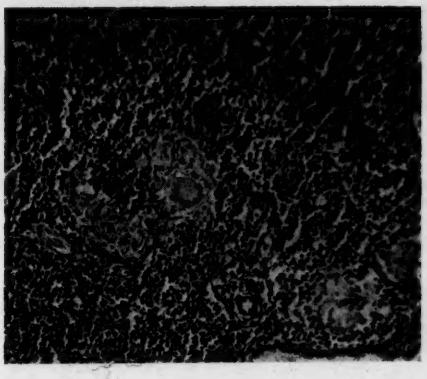


FIG. 4a.

Tissue from tonsil, just under the epithelium. Specific infiltrates with light cells whose structure in places resembles that of epithelioid elements, in other places are more like fibroblasts. A giant-cell is seen in such a focus. Just outside the lymphoid border medium-sized arterioles with fibrous thickened adventitia are found. (70×.)

Summary: In a 14 year old female, who reacted meningeally to cow-pox vaccine at 7 years of age, but has otherwise always been of good health previously, there developed a torpid, indolent, monocular nodular iritis, which in the course of a year or so reduced the vision to 2/60 and threatened perforation. Though the patient showed no pulmonary symptoms at all, an enlarged hilus shadow has developed during the same period into miliary, universal Roentgen shadows. Mantoux, ÷ (1 mgr.). Spontaneous recovery of the eye in the course of 3 or 4 years, ending in acuity of vision: 6/12. Considerable spontaneous healing of the

pulmonary alterations—all this not influencing general condition and tuberculin reaction. Diagnosis: Boeck's disease proved histologically on tissue taken from an apparently sound tonsil.

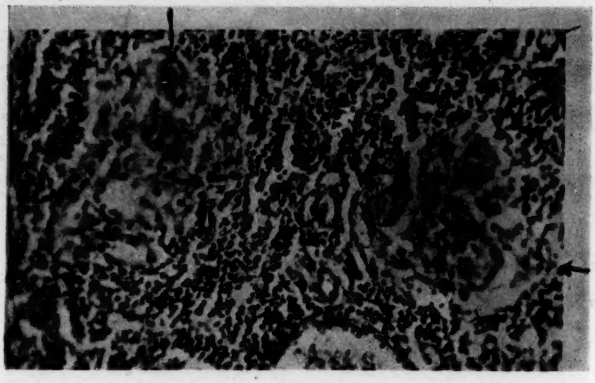


FIG. 4b.

Photograph showing the close connection between vessels and epithelioid foci. (156×.)

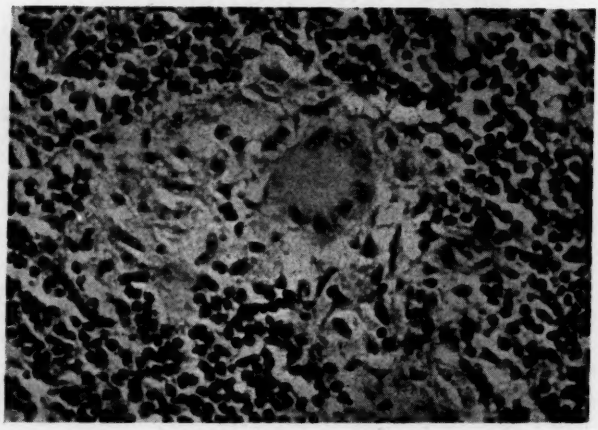


FIG. 4c.

Further magnification of minute portion of the same focus as shown in Fig. 1. The little vessels are seen almost to reach the giant-cell. (280×.)

In the eye department of the Kommunehospital of Copenhagen a case has been observed which offers points of resemblance with the above-mentioned so striking that I have asked the permission of the chief physician, Dr. E. Holm, to mention it in this connection.

A man, aged 21 years, previously in good health, of a sound family, suddenly develops an iritis in the right eye, with one single hyaloid nodule, large precipitates, opacities and a slightly blurred optic disc. Stethoscopy: slight dullness and bronchial breathing, no râles, which seems strange, as compared with X-Rays of lungs, which exhibit extensive exudative processes in both lungs. Mantoux: ÷ up to 1 mgr. No tubercle-bacilli in ventricle rinsing found by microscopy, cultivation or inoculation on guinea-pigs. Sedimentation rate: 10 mm. (1 hour). Though the patient feels perfectly well, is increasing in weight and apyretic, more nodules develop—after 70 days' illness there are 7, the visual acuity is 6/18—the same as 3 weeks after the outbreak of the disease.

After the iritis has persisted for about 120 days a sudden dissemination of numerous fresh nodules, and reduction of vision to counting of fingers at 1 metre. Steth. and X-ray of lungs: unchanged, X-ray of the skeleton of hands and feet: nothing abnormal: *repeated test excisions from the tonsils: nothing abnormal.* On the 120th day of illness: perfectly comfortable, absolutely fit (the patient is a music-hall artist). Left eye: perfectly natural. Right eye: acuity of vision, counting fingers 1 m. More peripheral corneal opacities with thickening of the parenchyma and ingrowth of deep vessels. Numerous large precipitates. Aqueous flare: 2·75. Scores of small hyaloid iridian nodules, with a localisation quite different from the one formerly described. The previously existing nodules, now vanished, have not left any atrophy of the stroma of the iris. Ophthalmoscopy: diffuse reflex of fundus.

In this case there is found: an interstitial keratitis, an iridocyclitis and possibly an optic neuritis in the right eye and a pulmonary affection, demonstrable by Roentgenology. The disproportion of the subjective disturbances to the objective findings is very striking both as regards the eyes and the lungs. Mantoux: ÷ 1 mgr.

The case of iritis Boeck here reported is peculiar in several respects. Only Plancherel's and Weidmann's cases, both of which are reported very briefly, have been monocular iritis. One would expect that universal diseases such as tuberculosis and morbus Boeck would be most likely to affect both eyes, and indeed, as seen by the table, this is the predominating fact.

Further, in the reported case there are strikingly few symptoms. Nevertheless the diagnosis could be made by microscopy of a clinically quite normal tonsil, and the case thus supports the emphasis which Schaumann lays on the value of this method of investigation (even though the case of the Kommunehospital raises the question whether the tonsils are *always* affected).

Finally, there is reason for calling attention to the patient's hypersensitivity to cow-pox vaccine and her brother's death in connection with vaccination. Very little is known about the deeper causes of vaccination deaths, but a constitutional hypersensitivity is suspected to be at the bottom. Boeck's disease is considered by such investigators as Kissmeyer and Lemming, etc., to be a special, constitutionally conditioned tissue reaction, a theory which shall not be further discussed here. In the present

TABLE

	Author	Age, sex	Skin	Parotid	Submaxillaris	Conjunctiva	Cornea	Iris		Choroid	Lens	Tension
1	1909 Schumacher	42 ♀	+	+ +	+ +	...	...	+ +	nod.	...	...	..
2	1910 Bering	37 ♀	+	+ +	+ +	...	...	+ +	nod.	...	...	...
3	1912 Unna	34 ♂	+	...	...	...	...	+ +	...	...	...	...
4	1913 Broers	—	+	...	...	...	...	+ +	...	...	...	...
5	1914 Plancherel	—	+	...	...	...	+	+	serous	...	...	...
6	1915 Bloch	67 ♀	+	...	...	...	...	+ +	...	...	...	...
7	1915 Ehrmann	—	+	...	...	...	...	+ +	...	...	...	..
8	*1919 van Husen*	—	+	...	+	...	...	+ +	...	...	...	...
9	1920 Schoeppe	—	+	...	...	...	+ +	+ +	...	...	+ +	...
10	1922 Weidmann	21 ♂	+	...	...	...	...	+	...	...	...	...
11	1923 Favauge-Bruyel	16 ?	+	...	...	...	...	+ +	nod.	...	+ +	+
12	,,	18 ?	+	...	...	...	...	+ +	serous	+ +	...	...
13	,,	48 ?	+	...	...	...	...	+ +	nod.	...	...	...
14	,,	65 ?	+	...	...	...	...	+ +	nod.	...	...	+
15	,,	19 ?	+	...	...	...	+ +	+ +	nod.	...	...	...
16	1924 Savatard	—	+	...	...	...	...	+ +	...	...	...	...
17	1924 Martenstein	—	+	...	...	...	...	+ +	...	...	...	...
18	1925 Hudelo and Rabut	—	+	...	...	...	...	+ +	...	+ +	...	...
19	1927 Habermann	21 ♂	+	...	...	...	...	+ +	...	...	...	...
20	1928 Mylius	24 ♂	...	...	...	...	...	+ +	nod.	...	...	...
21	1933 Funk	—	+	...	...	...	...	+ +	...	...	...	...
22	1934 Ramel	—	+	...	...	...	...	+ +	...	...	...	...
23	1936 Sandbacka-Holmström	39 ♀	+	+ +	+ +	...	...	+ +	...	...	...	+
24	*1936 Grönblad*	25 ♀	+	+ +	+ +	+	...	+ +	nod.	...	...	...
25	,,	53 ♂	...	+ +	...	...	...	...	...	...	...	...
26	1937 Nordin	26 ♀	+	...	...	...	+	+ +	nod.	...	...	+
27	1937 Own case	15 ♀	...	...	...	...	...	+	nod.	...	...	...

TABLE—*continued*

	Neuritis optica	Lungs	Liver	Spleen	Bones	Allergy	Histological diagnosis	Complications, Course
1	...	...	...	...	...	+ +	+	.....
2	...	...	...	...	...	+ +	+	.....
3	...	...	...	...	...	+	+	.....
4	...	...	...	...	...	.....	...	*Peritoneal tuberculosis*
5	...	...	...	...	...	.....	+	Spontaneous recovery—½ year
6	...	...	...	...	...	+ (Pirquet)	...	.....
7	...	...	...	...	...	.....	...	.....
8	...	...	...	...	...	+ (Pirquet)	...	Phthisis bulbi, o.u.—2 years
9	...	+	...	...	...	.....	+	.....
10	....	...	...	...	...	.....	+	+ W. R.
11	...	...	+	+	...	+ (Pirquet)	...	Progressive spinal atrophy
12	+ +	...	+	+	...	+ (Pirquet)	...	.....
13	...	...	...	...	...	.....	...	.....
14	...	+	...	...	...	+ (Pirquet)	...	.....
15	+ +	+	...	...	...	+ (Mantoux 0,7)	...	.....
16	...	...	...	...	+	.....	...	.....
17	...	...	...	...	...	+ (Moro)	...	.....
18	...	...	...	...	...	.....	...	.....
19	...	+	...	...	...	+ (Pirquet)	...	.....
20	...	+	...	...	+	+ (Pirquet)	+	Left eye: phthisis—1 year. Right eye: remission—2 years, new dissemination. phthisis 2 years
21	...	+	...	...	+	.....	...	Skin and eyes recovered simultaneously with outbreak of pulmonary tuberculosis
22	...	...	+	...	...	+ (Moro, Pirquet)	+	9 years after. V. perception of light
23	...	...	...	...	+	+ (Mantoux 1,0)	+	.....
24	...	...	...	...	...	+	+	.....
25	...	...	...	...	...	.....	...	Parotid and uvea: Total recovery in few months. Dermal affection 6 years afterwards
26	...	+	...	...	+	+ (Mantoux 0,1)	+	.....
27	...	+	...	...	+	+ (Mantoux 1,0)	+	.....

state of research no kind of evidence is forthcoming for the existence of a connection between these phenomena, but it appears to me that such a connection is very possible. Bering tells us that the patient observed by him had a sister who died suddenly at 7 years of age from "Gehirnschlag."

To tell an iritis Boeck from an iritis tuberculosa by the look of it is hardly possible. The differential diagnosis must be based on the general condition of the patient, tuberculin reaction, Roentgenograms and probatory excisions.

The Boeckean iritis is peculiarly painless, it may remit and disappear, so to say, into space; on the other hand, it may also destroy the eye through new attacks. Further, Boeck's disease seems to affect the iris itself preferentially, and to involve the choroid and optic nerve less frequently than tuberculosis.

It has been alleged that iritis or iridocyclitis is of common occurrence in Boeck's disease. This is of some moment with a view to the relations, much disputed at the present day, between Boeck's disease and uveo-parotid fever (Heerfordt). Exact statements, however, are sparse.

Duke-Elder[7] asserts that Kissmeyer has found iritis in 5 out of 20 cases of Boeck's disease. This, however, is due to a misunderstanding: in Kissmeyer's paper cited, the author remarks that Bloch[3] has collected 5 cases of iritis among 20 cases of morbus Boeck; but states expressly that he himself has not observed a single case of iritis (18, p. 71: "Nous n'avons observé aucun cas d'iritis"). Blegvad[2] mentions the cases which are noted in the table on p. 156 under Nos. 1, 7, 17, 18, 19 and 9, and asserts that in going through the literature one finds iritis or iridocyclitis in about 10 per cent. of all the cases of Boeck's disease. In my list 27 cases of iritis in Boeck's disease are tabulated. These cases, as may be seen from the references, have been drawn mostly from dermatological publications. I have not aimed at an exhaustive review of the literature; and to a critical classification of the dermatologic symptoms I have not felt competent. But in the portion of literature I have managed to go through, I have found about 400 cases of certain or supposed Boeck's sarkoid without eye symptoms. If to this we add that the ophthalmological symptoms are described very briefly and vaguely in several of the tabulated cases, that a number of the patients have had tuberculosis or other diseases in combination with Boeck's disease, that some of the cases have not been histologically verified, and that others are included because histologically they have been classified as Boeck's sarkoid though clinically the designation uveo-parotid fever (Heerfordt) would seem obvious, I think we may reasonably consider the previous estimates as having been too high. On the basis of an ampler material iritis must be said to be a relatively

rare symptom in Boeck's disease, the rate of frequency being between 5 and 10 per cent. of the cases, probably nearest the 5 per cent.

Iritis Boeck, like tuberculous iritis, is a torpid inflammatory condition with a tendency towards nodulation. No doubt it is true that the two diseases are not differentiable morphologically. In the case described above the nodules grew into a quite unusual size (Fig. 2). Also the slight disturbance caused to the patient was strange. As the lack of reaction from the tissues and necrosis are characteristic of Boeck's disease, it is probable that the said peculiarities have not been accidental, but are characteristics of iritis Boeck. (Bering, Favauge-Bruyel and Nordin describe the nodules as very large.)

Iritis Boeck seems little liable to such complications as choroiditis or neuritis optica. The few cases in which such complications have been described, are somewhat briefly reported—that the complications *may* occur, cannot reasonably be doubted, and besides they have been histologically demonstrated in Mylius and Schürmann's case.

The course of iritis Boeck, it seems, may be either (1), as in the above case and those of Plancherel[27] and Grönblad,[11] rapid spontaneous recovery, so that even very large nodules disappear without leaving any scars, which would hardly be conceivable in tuberculous iritis; or (2), as in van Husen's and Mylius's cases: a dissemination of iridian nodules, after which the condition remains stationary or improves during a long period of time, then a new seeding out of nodules takes place, after which the eye becomes phthisic. No perforation has been described in contrast with cases of iridian tuberculosis.

It seems to me that the available material is extensive enough to justify the following inferences: A distinct iritis Boeck exists which is not identical with tuberculous iritis. Iritis Boeck is less painful, less destructive and more proliferative than the latter disease. Morphologically the individual case cannot be distinguished from tuberculous iritis; the differential diagnosis can only be made clinically by observation of the general condition, allergic reaction, contingently by biopsy or Roentgenography of such organs which are found most frequently to be affected by Boeck's disease.

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NIGHT BLINDNESS

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THE interest which has recently been focussed on the problems of nutrition has resulted in a widespread search for quick, easy and reliable methods for measuring small degrees of dietary deficiencies.

Although the connection between vitamin A deficiency and night blindness has been well established for some time, it is only quite lately that the taking of dark adaptation curves has been much used as a test for slight degrees of malnutrition due to a deficiency of this vitamin. Unfortunately, by far the greater part of the work done on these lines is entirely unsatisfactory from the visual side—in fact it is probably not going too far to say that most of the dark adaptation curves, taken with a view to estimating the degree of vitamin A deficiency in a given individual, are quite worthless.

This deplorable state of affairs seems to be due to the sudden incursion of clinicians and vitamin workers into the highly specialised field of subjective visual research. The necessity for some previous training in what is, after all, an extremely complicated and difficult experimental method has not, apparently, been realised. In some cases, even, the very reasons for using a dark adaptation test at all for the measurement of vitamin A deficiency seem not to have been fully understood.

The purpose of this paper is to restate, as simply as possible, what we know about night blindness and why we should expect one type of this disease to be curable by vitamin A therapy. It is not intended to indulge in an exhaustive criticism of the work that has already been done but rather to point the way to that better general understanding of the whole subject without which really satisfactory work cannot be achieved. A few general criticisms of the methods at present in vogue will be found at the end of this paper.

It is on circumstantial evidence only that we base the belief that our visual perceptions at low illuminations are the result of the reactions of visual purple to light. If, however, we take all the facts together not only do they make an extremely convincing case, but, up till now, nothing has emerged from the study of visual purple which might cause us to look on this theory with suspicion.

The duplicity theory is, in the main, the work of three men—Schultze (1866), Parinaud (1881) and v. Kries (1896), but it is probably easier to show on what exactly we base the complete theory to-day if we neglect the chronological order of the various discoveries and take the steps in the order in which they make the most connected story.

The duplicity theory has to explain why there are such remarkable differences between our vision at illuminations over 0·01 f.c. (day vision) and our vision at illuminations below this level (night vision). At high illuminations we can appreciate colour (differences in wave length) and the most sensitive part of the retina is the fovea which we use for all activities requiring distinct vision. At low illuminations we are colour blind and find that, while the fovea is comparatively insensitive, the sensitivity of the peripheral retina is enormously increased. In day vision the brightest part of the spectrum appears to be in the " yellow," but at night, while the spectrum is appreciated in shades of grey only, the brightest part has shifted to the " green " and the " red " is entirely invisible. This change-over is known as the Purkinje (1825) phenomenon and occurs only in the periphery. At low illumination the fovea is unable to see the spectrum at all until it is made bright enough for the colours to appear. Even in day-light vision the extreme periphery of the retina is practically colour blind. The first step, then, connects the fovea with the acute coloured vision characteristic of high illuminations, and the peripheral retina with the colourless vision of low ones. The fovea is most sensitive to a wave-length of 555mμ (yellow), but can be stimulated by all parts of the visible spectrum while the periphery (in the dark adapted eye) is most sensitive to those between 500 and 505mμ (green) and not at all to those longer than 650mμ (red).

Careful microscopic study of the retina reveals that the fovea and periphery are of different histological composition. The fovea is made up entirely of cones while around it the cones become mixed with rods and, in general, as we go farther out towards the periphery the relative number of rods to cones becomes progressively higher. In the human retina the actual number of visual elements decreases towards the periphery so that although the ratio of rods to cones increases the actual rod count is highest in a ring at about 20° from the fovea (Osterberg, 1935). Therefore, the second step in our chain of evidence connects the cones with day vision and the rods with night vision. This view is borne out by the fact that animals that live mostly by night or in dark places have a great predominance of rods in their retinae while animals that spend much time in the sun have mostly cones. This relationship between the rod and cone content of the retina and habit has been well demonstrated by Detwiler (1923) and

Kolmer (1930) on lizards and primates respectively (see also Walls, 1934).

According to our present ideas an end-organ must contain a photo-chemical substance if it is to be capable of stimulation by light, and this is where the story comes to an end, for the present, as far as the cones are concerned for although Studnitz (1932 and 1937), Wald (1937), and Chase (1938) all claim to have extracted a pigment from the cones the amounts have been so small that no satisfactory investigation has so far been possible. Incidentally it appears that these three workers are not all dealing with the same pigment.

Boll (1876) first observed a red pigment in the retina which was bleached by light but it was Kühne (1877) who called it visual purple and showed that it was to be found in the rods only and that the retinae of animals in which rods predominate were particularly rich in this substance. He was unable to find any in the retinae of those species of snake and lizard which he examined. Later Köttgen and Abelsdorff (1896) plotted the absorption curve of visual purple and Trendelenburg (1911) made a curve of the bleaching power of different wave-lengths for visual purple. Both these curves practically coincide as one might expect from Draper's Law but they also agree pretty well with the curve of the sensitivity of the dark adapted eye to the different parts of the spectrum. Thus, corresponding to the maximum sensitivity of the rods to the green and the absence of sensitivity to the red wave-lengths visual purple is most readily bleached by green and is unaffected by red light. König (1894) also pointed out the significance of the similarity of the absorption curve of visual purple to the luminosity curve of the dark adapted human eye. Recently Dartnall and Goodeve (1937) have recalculated the luminosity curve at low illuminations on a quantum basis and compared the results with Lythgoe's (1937) visual purple absorption curve. They have found these two curves to be practically identical. So our third step connects the bleaching of the photo-chemical substance, visual purple, with vision at low illuminations.

In the eye visual purple is bleached by light but reappears slowly in the dark (Kühne found two hours necessary for regeneration in the frog and 38 minutes in the rabbit); at the same time the eye becomes slowly more sensitive during a stay in the dark and, therefore, since the effect of a given amount of light on a photochemical substance is proportional to the concentration of the substance it seems probable that the regeneration of visual purple is responsible for dark adaptation.

The condition known as night blindness is simply a failure in dark adaptation. In some cases the failure appears to be due to a slowing of the process and the patient merely takes longer to

reach the normal level, while in others the normal level is never reached at all. v. Kries himself considered that night blindness was caused by a failure of the rod apparatus just as complete colour blindness was due to a failure of the cones. Parinaud did a good deal of work on the light sense and colour sense in night blindness and considered that the relations found in this disease formed one of the most essential supports of the duplicity theory. He believed the poor dark adaptation in this condition to be due to a faulty regeneration of visual purple which prevented the eye from reacting to low illuminations.

Night blindness has been recognised since pre-Christian times, and there is an immense body of literature from all over the world describing its symptoms and treatment. There have been many contradictory theories and much controversy as to the aetiology of the disease but we can now divide the cases into two main groups—those in which the night blindness has, so far, proved incurable and those in which it can be cured. Both simple congenital night blindness and the night blindness which characterises the early stages of retinitis pigmentosa, come into the first group while the night blindness sometimes associated with jaundice, with diseases of the liver or with malnutrition, come into the second. In the cases which may be included in the first category the retinal defect seems to be due to an abnormality of the rod cells themselves while in those belonging to the second the defect appears to be in the visual purple mechanism and the rods may be otherwise perfectly normal.

No histological examinations of the retina in cases of congenital night blindness have been made but in retinitis pigmentosa it seems to be established that the rods are the first cells in the retina to be affected (Treacher Collins, 1919, Verhoeff, 1931). Unfortunately there are no preparations available of eyes in which the disease is still in the early stage where night blindness is the only symptom. In a strain of rats which bear an hereditary disease of the retina histologically indistinguishable from human retinitis pigmentosa it has been shown that the earliest detectable change is the death of the rod cells and that visual purple is still present in the degenerate outer limbs several weeks after every rod nucleus in the retina is dead (Bourne, Campbell and Tansley, 1938). It is obvious, therefore, that it is futile to attempt to cure the night blindness of retinitis pigmentosa by treatment with carotene or vitamin A, since although these substances can improve the production of visual purple where this is deficient they are unable to repair degenerated rods (Tansley, 1936). It has, in fact, been shown that injections of carotene have no effect on the development of the retinal degeneration in rats (Bourne and Tansley, unpublished observations).

The night blindness which may occur in jaundice or in liver

disease seems to be due to the same cause as that which is produced by malnutrition—namely vitamin A deficiency—and in all these conditions the defect can be cured by vitamin A therapy. In obstructive jaundice the trouble seems to be due to a deficient absorption of fats and therefore of vitamin A and carotene from the intestine (Blegvad (1924), Greaves and Schmidt (1935)) and it may be necessary to give injections of vitamin A although the visual symptoms disappear if the jaundice clears up (Baas, 1894, Hess, 1909, Bloch, 1924, and many others). It has been observed by Wright (1931) Owen and Hennessey (1932) and others that symptoms of vitamin A deficiency, including night blindness, may appear in an apparently well-nourished individual as a sequel to liver disease. In these cases the liver appears to be unable to convert the carotene of the diet into vitamin A.

Another condition which may be associated with night blindness is pregnancy but only if the diet is rather poor in vitamin A. The reason seems to be that the female requires more vitamin A during pregnancy and a dietary level which is sufficient for good health normally may not be high enough under the added burden of providing for the foetus (Tansley, 1936). Many cases of night blindness during pregnancy were reported from Vienna during the famine years after 1918 (Birnbacher and Klaften, 1923, Klaften, 1923).

The connection between night blindness and vitamin A deficiency is now so well established and so widely accepted that it is not necessary to go into the literature here, fascinating though much of it is. It has been known all over the Old World for many hundreds of years and especially to primitive peoples that night blindness can be easily and rapidly cured by eating liver, and during the last twenty years it has been established that it is the vitamin A present in liver which is the curative factor. Holm (1925) and Sugita (1925) both demonstrated that vitamin A deficient rats were not able to get about at low illuminations as well as normal controls, and lately Hart and his co-workers in California (Hart, Mead and Guilbert (1933), Guilbert and Hart (1934 and 1935), Hart and Guilbert (1937), and Guilbert, Miller and Hughes (1937)), in a series of magnificent investigations into vitamin A deficiency in domestic animals have come to the conclusion that night blindness is the very first symptom of this condition and that the vitamin level which can just protect an animal represents the true physiological minimum requirement.

Since vitamin A deficiency causes night blindness both in man and animals one would expect it either to affect the production of visual purple in the dark-adapted retina or to cause degeneration of the rods. The rapidity with which nutritional night blindness can often be cured with vitamin A (Aykroyd, 1930), would

indicate that the effect is more likely to be on the visual purple, since the repair of a damaged tissue would be expected to take more than a few hours. In point of fact it has been shown experimentally that the regeneration of visual purple is retarded and may be prevented as a result of deprivation of vitamin A. Fridericia and Holm (1925) found that the increase in visual purple content of the retinae of vitamin A deficient rats during a stay of three hours in the dark was always lower than that of normal controls. They compared the colours of the whole retinae with a modification of Garten's (1906) colour chart of the bleaching of visual purple. Their results were confirmed by Tansley (1931) who measured the optical density of visual purple extracts at intervals during dark adaptation. In this way curves for the regeneration of visual purple in normal and deficient rats were obtained and the latter always showed a decreased production of visual purple during a stay in the dark. Incidentally, the regeneration curve for normal rats obtained by Tansley was very similar to the human dark adaptation curve and therefore provides another piece of evidence that dark adaptation is due to the regeneration of visual purple. It has also been shown (Tansley, 1933 and 1936) that vitamin A deficiency prevents the production of visual purple in the developing eye and that although it may cause slight degenerative changes in the rods these are always a later development. There is a possibility that if the deficiency is allowed to become severe enough to affect the rod structure the resultant night blindness is, in fact, incurable (Hart and Guilbert, 1937, and Tansley—unpublished observations on Hart's material).

It is now necessary to inquire into the mechanism by which vitamin A is able to affect the production of visual purple. Holm (1929), in a paper which has not received the attention it deserves, was probably the first to suggest that visual purple may be closely allied to vitamin A and may, in fact, be formed from it. He was not, however, at all certain that this is the case since vitamin A and visual purple have such different chemical properties and since visual purple can be found in vitamin A deficient retinae provided the animals have been kept in the dark during the period of deprivation.

Wald (1935) as a result of experiments on the pigments which can be extracted from light and dark adapted retinae produced a scheme for the production and breakdown of visual purple. He believed that visual purple is a protein conjugated with a prosthetic group, the action of light being to split the molecule at this connection. Further, he stated that this breakdown produces a protein and a carotenoid pigment which he called retinene, and that retinene then forms vitamin A by an ordinary chemical reaction. This vitamin A can recombine with the protein in the

dark and visual purple is formed again. This is an extremely attractive theory but unfortunately it still remains unconfirmed. Krause and Sidwell (1938) could find no evidence that vitamin A is produced as a result of the breakdown of visual purple and although they also believe that visual purple is a conjugated protein they are doubtful whether the prosthetic group is, in fact, a carotenoid. Recently (1938) Wald has modified his original theory thereby bringing it more into line with the results of other workers.

It should now be clear why the measurement of dark adaptation might be expected to give information as to whether or no an individual is satisfactorily provided with his vitamin A requirements. In an investigation on human subjects made deficient in this vitamin Booher, Callison and Hewston (1938) have clearly shown that the dark adaptation curves are affected and further that they can be brought back to normal by the administration of vitamin A. Haig, Hecht and Patek (1938) have taken dark adaptation curves from a patient suffering from cirrhosis of the liver and therefore probably from vitamin A deficiency as well. They found that the adaptation of this patient was markedly inferior to that of normal subjects but that it could be brought up to the normal level by injections of vitamin A. Both these groups of workers found that although the deficient curves are inferior to the normal ones at every point during a stay of thirty minutes in the dark the differences are far more obvious at the end of the experiment than at the beginning and Booher and her co-workers definitely point out the danger of trying to estimate the degree of vitamin A deficiency, particularly where this is slight, on the basis of readings taken after a short period of dark adaptation.

Many workers mostly in America, Denmark and this country (Frandsen 1934, Jeans and Zentmire 1936, Jeghers 1937, Edmund and Clemmesen 1937, Maitra and Harris 1937, Mutch and Griffith 1937, and others) have attempted to evaluate the extent of vitamin A deficiency in sections of the population by the examination of the dark adaptation of large numbers of individuals and have all come to the conclusion that there is a widespread failure to reach a satisfactory standard. Unfortunately the experimental procedure of much of this work is open to serious criticism and the results have not been confirmed by other workers whose investigations have been more carefully controlled (Ehlers 1937, Groth-Peterson 1938, Palmer 1938). Some of the more obvious criticisms may be mentioned here. In many cases the subjects are only tested twice, once to get the initial level and once more after vitamin A therapy and it is not surprising that the second readings should be better than the first since there is known to be improve-

ment with practice. Again there seems to be no appreciation of the wide individual and day to day variations which are found even in subjects who have been provided with good doses of vitamin A for some time before the curves are taken. The effect of the general level of light adaptation, which often depends on the weather and which seems to influence the results even when a preliminary exposure to high illuminations forms part of the experiment, has not been taken into account. Another important factor, which has been almost completely ignored, is the aperture of the pupil which is normal to the subject during light adaptation. This has been found to be the chief cause of variation in the dark adaptation curves of a collection of normal subjects all of whom were provided with extra vitamin A before they were investigated. (Investigation of the dark adaptation curves of medical students at University College, London, by L. R. Phillips.)

Also, in spite of the fact that vitamin A deficiency is known to have much less effect on the early than on the later part of the dark adaptation curve, most of the measurements have been made during the first ten minutes in the dark in order to save time. It has already been mentioned that Booher, whose work has been unusually carefully done, does not consider that these early readings can give satisfactory results.

Vitamin A deficiency is believed to result in poor dark adaptation because it causes a poor regeneration of visual purple in the retinal rods, yet most of the investigations have, in fact, been made under conditions where the central part of the retina, which contains no rods, must be used! In point of fact, this criticism is not so serious as appears at first sight since there is some evidence that vitamin A also has some influence on cone adaptation. Normal dark adaptation can be divided into two parts, an early adaptation, probably due to the cones, which is not very great in extent, and is complete in about seven minutes, and a later rapid and extensive adaptation which is due to the rods. Since most workers take their readings during the first ten minutes they may very well be testing cone adaptation only, even when they use an area of the retina which also contains rods. There is no doubt that the early cone adaptation is impaired by vitamin A deficiency though to a much less extent than the rod adaptation (Booher *et al.*, Haig *et al.*) and Hecht and his colleagues believe that this effect on the curve indicates that vitamin A must be necessary for the formation of the cone substance in the same way that it is known to be necessary for the formation of visual purple. Whether this is so or not, it would seem to be more sensible, when testing for vitamin A deficiency by taking dark adaptation curves, to use a part of the retina which is known to

contain rods and visual purple, even if to do so entails the spending of more time and trouble on the observations.

There is no doubt at all that variations from the normal dark adaptation curve can be used to diagnose vitamin A deficiency provided the test is made by experienced observers with suitable apparatus and over a sufficiently long period of dark adaptation. It is, however, extremely doubtful whether this particular method can ever be of any great value under the conditions which obtain when wide nutritional surveys of populations are attempted. In order to obtain a reliable dark adaptation curve the services of a skilled experimenter with elaborate apparatus are an absolute necessity and at least an hour is required for each individual test. These conditions are obviously not attainable when several hundred subjects have to be tested over a relatively short period.

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THE CHEMICAL EQUILIBRIUM OF THE INTERSTITIAL FLUIDS AND THE AQUEOUS HUMOUR*

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THE chemistry of the various biological fluids is of importance, for chemical analysis is another method of determining the nature of the various fluids throughout the body. It is proposed to limit the discussion only to certain aspects of this problem, namely:—

1. The chemical equilibrium that exists between blood and lymph.

2. The chemical equilibrium that exists between blood and gastric juice.

3. The chemical equilibrium that exists between blood and the aqueous humour.

* Lecture delivered at the Royal London Ophthalmic Hospital, November 18, 1938.

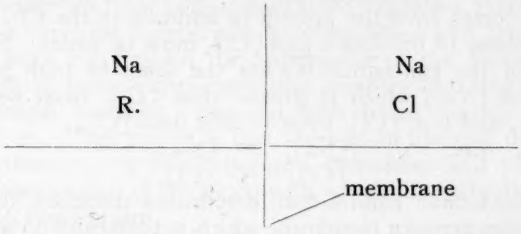
The first is an example where simple dialysis or ultra-filtration alone play a part in the production of the fluid. The simple physical laws governing the production of dialysates have already been described—Robertson (1939).

The second is an example of a typical secretion.

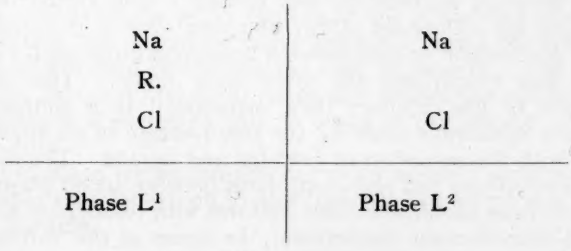
The third we shall call the unknown.

Before going on to a general discussion of the chemistry of these different fluids of the body, I would like very briefly to refer to the Donnan equilibrium, or as it is sometimes called—the Gibbs-Donnan equilibrium.

This term is mentioned a great deal when chemical analyses are being discussed, and it is usual for most text-books to describe it in the following way. The following diagram represents two electrolytes NaR. and NaCl separated by a membrane indicated by this vertical line.



Let us assume that these solutions have just been separated from one another by this membrane. Now if the membrane does not allow the anion R. of the salt NaR. to pass through it, but allows all the other ions and salts to do so, then when equilibrium has been established, the following will be the state of the various ions.



The solution containing the impermeable anion R. to the left of the above membrane is known as " phase L^1," while that on the other side is known as " phase L^2."

In a word, the Gibbs-Donnan theory of equilibrium put very simply is this.

"The product of any pair of diffusible cations and anions on one side of the membrane is equal to the product of the same pair of cations and anions on the other side"—or that—

$$[Na]_1 \times [Cl]_1 = [Na]_2 \times [Cl]_2$$

where the concentrations of Na and Cl are expressed in grams molecules per litre of solutions.

On the side of the membrane containing the non-diffusible substance R $[Na]_1$ is the sum of:

1. The cations formed by the splitting up of NaR.
2. The cations formed by the splitting up of NaCl.

On the other side of the membrane $[Na]_2$ is the concentration of cations only in combination with $[Cl]_2$.

It therefore follows from the above that in the phase L^1 the concentration of $[Na]_1$ must exceed that of $[Cl]_1$ (because some of the Na comes from the protein in addition to the Cl).

In the phase L^2 the $[Na]_2$ and $[Cl]_2$ must be equal. Since the products of the concentrations are the same in both phases it follows that $[Na]_1$ which is greater than $[Cl]_1$ must be greater than $[Na]_2$ and that $[Cl]_1$ must be less than $[Cl]_2$.

i.e., $[Na]_1 > [Na]_2$

$[Cl]_1 < [Cl]_2$

The Gibbs-Donnan equilibrium, determines therefore, the distribution of ions across a membrane which is permeable to some ions and impermeable to others. Many experiments carried out *in vitro* between protein and salt solutions with semi-permeable membranes have confirmed the equilibrium described above—namely, that on the side of the membrane where there is protein, the cations—*e.g.*, sodium is greater than on the other; and again, the anions—*e.g.*, chloride are greater on the side of the membrane where there is no protein.

This chemical equilibrium was carried a step further by van Slyke and his colleagues (1925) who employed it to explain the uneven distribution of ions between biological fluids such as blood plasma and lymph and the other body fluids. The vascular membrane of the capillary they maintained is a simple semi-permeable membrane allowing the free passage of all anions and cations with the exception of proteins and lipoids. The distribution of electrolytes and non-electrolytes between blood plasma and its ultrafiltrates should therefore conform with reasonable accuracy to the Gibbs-Donnan predictions. In terms of the various substances present in blood, the Gibbs-Donnan predictions are:—

1. Freely diffusible non-electrolytes such as non-protein nitrogen, urea, uric acid, creatinine and sugar are evenly distributed between plasma and its ultrafiltrates.

2. On the blood side of the capillary membrane one would expect more cations such as sodium, potassium, calcium, and magnesium.

3. On the ultrafiltrate side of the membrane there should be more anions such as phosphate, chloride and sulphate.

4. The product of any pair of diffusible cations and ions on one side of a membrane is equal to the product of the same pair of cations and anions on the other. For the purposes of this equation we shall adhere only to the simple product of Na and Cl.

The Chemical Composition of Lymph.—It is generally recognised that lymph is formed from blood plasma by simple filtration through the capillary wall. That being so the chemical composition of lymph should resemble that of an ultrafiltrate of blood dialysed *in vitro*. Since 1925, several workers have made complete chemical analyses of lymph and chief among these has been Drinker and his colleagues (1935) (1933) at Harvard. In making a chemical comparison between blood and lymph, these workers have emphasised the importance of the following conditions which many experimentalists completely disregard.

1. Lymph must be compared with blood *plasma*—not with *whole blood*. The reason is that there is an unequal distribution of substances in the blood between corpuscles and plasma and it is the plasma part of the blood with which the body fluids would come into equilibrium.

2. The values for the various substances must be expressed in terms of the water contents of the fluids. This correction is most important where there is a protein molecule on one side of the membrane and not on the other. The protein molecule is so large that its water displacement may introduce an error.

To give an example.—100 c.c. of blood cells contain only 72 grams water. 100 c.c. of blood plasma contain only 93·5 grams water. 100 c.c. of cerebro-spinal fluid contain 99·6 grams water. The variations in the water content is due to the fact that blood cells contain 32·3 grams per cent., plasma 7 grams per cent., and cerebro-spinal fluid 0·02 grams per cent. of protein. The protein molecule, therefore, takes up space and dilutes the concentration of substances if estimated only in terms of per 100 c.c. of a particular fluid.

3. Blood and lymph samples can never be taken simultaneously for it takes time for lymph to flow from the site where it is formed to the cannula.

Chemical Composition of Lymph

1. *Protein.*—The first point of importance is that there is less protein present in lymph than in blood plasma. This gradient in the protein concentration is not unexpected, for the capillary

membrane is a so-called semi-permeable membrane and holds back the plasma proteins. It is probable that if a sample of tissue fluid was obtained—that is the fluid as it filters through the capillary wall, it would contain less protein than that of lymph, because the absorption of water and salts by the capillary wall tends to increase the concentration of any protein in the tissue spaces; and it is the unabsorbed fluid that is left in the tissue spaces that enters the lymphatic capillaries to become lymph. Unfortunately, it is not possible to get samples of tissue fluid. However, other than their protein content, there can be little difference in the respective chemical compositions of lymph and tissue fluid.

2. *Freely diffusible non-electrolytes.*—Most workers agree that in animals under normal conditions, freely diffusible substances such as non-protein nitrogen, urea, creatinine, uric acid and sugar occur in almost identical concentrations in the plasma and lymph. The following tables (1 to 3) from analyses by Arnold and Mendel (1927) give comparisons between the sugar and non-protein nitrogen of the lymph and blood plasma under various normal and experimental conditions.

COMPOSITION OF BLOOD PLASMA AND LYMPH OF A DOG

TIME		SUGAR	N.P.N.
7.30 a.m.	Plasma	126	27
8.0 a.m.			
10.0 a.m.	Plasma	124	27.2
11.0 to 1.0 p.m.	Lymph	124	27.0
1.0 p.m.	Plasma	125	27.3
1.0 to 3.30 p.m.	Lymph	123	26.4.
3.30 p.m.	Plasma	120	26.3
3.30pm.-4.30	Lymph	128	
4.30 p.m.	Plasma	117	

FIG. 1.

It can be seen from Fig. 1 that these substances occur in almost identical concentrations under normal laboratory conditions.

In addition to these observations on the intact animal, the changes in the chemical composition of lymph and blood have been studied after the various constituents of the blood have been artificially altered. It has been found that as the concentration of the various substances in the blood altered comparable changes occurred in the lymph at the same time There are several methods that have been employed to bring about these changes and they include :—

1. *Exclusion of the kidney function.*—The kidney function was excluded by ligation of the ureters and renal vessels and as a result the non-protein nitrogenous constituents accumulated in the blood. The following figure summarises the changes which occurred.

COMPOSITION OF BLOOD PLASMA AND LYMPH AFTER THE KIDNEY FUNCTION HAD BEEN EXCLUDED BY LIGATION OF URETERS AND RENAL VESSELS

TIME		SUGAR (mgs. per	N.P.N 100 c.c)
10.0 a.m.	Plasma	118	28.1
10.30 a.m.	Ureters and Renal Vessels Ligated.		
11.45 to 12.30 p.m.	Lymph	117	31.6
12.30 p.m.	Plasma	112	33.3
12.30 to 1.30 p.m.	Lymph	114	34.3
1.30 p.m.	Plasma	100	36.6
1.30 to 3.0 p.m.	Lymph	100	38.1
3.0 p.m.	Plasma	100	38.3
3.0 to 5.0 p.m.	Lymph	99	41.5
5.0 p.m.	Plasma	100	42.3

FIG. 2.

The table in Fig. 2 shows that as the non-protein nitrogen accumulated in the blood, so its concentration rose to the same degree in the lymph. It follows, therefore, that the interchanges of the non-protein nitrogen must take place very promptly between these two fluids. I should explain that the non-protein nitrogen includes constituents such as urea, creatinine, uric acid, amino-acid nitrogen.

2. *Injection of insulin.*—It is well known that soon after the subcutaneous injection of insulin the blood sugar begins to fall. The following table shows the sugar in the blood and lymph following insulin administration.

It can be seen from Fig. 3 that the lymph sugar intimately follows the fall in the blood plasma sugar. It is, of course, difficult to obtain exactly corresponding values because the lymph must be collected over a certain period of time. The following figure from the work of Heim and Berg (1933) shows the changes in plasma sugar and lymph obtained from the subcutaneous vessels at frequent intervals after the insulin injection. It will be noted that as soon as the insulin takes effect, the lymph sugar follows very closely that of the plasma.

COMPOSITION OF BLOOD PLASMA AND LYMPH AFTER THE INJECTION OF INSULIN

TIME		SUGAR (mg. per 100 c.c.)
3.0 p.m.	Plasma	140
3.30 to 4.30 p.m.	Lymph	143
4.30 p.m.	Plasma	139
4.45 p.m.	10 c.c. Insulin (200 units) Injected	
4.30 to 5.30 p.m.	Lymph	107
5.30 p.m.	Plasma	51
5.30 to 8.0 p.m.	Lymph	60
7.30 p.m.	Plasma	32

FIG. 3.

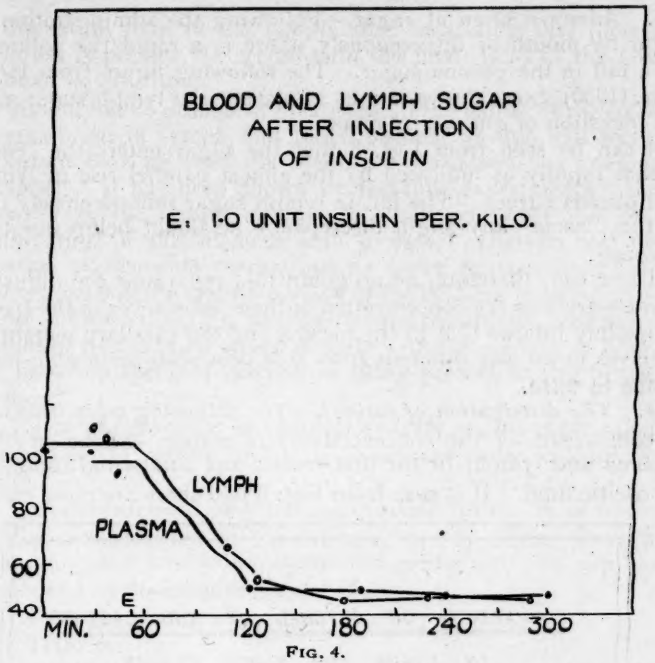

BLOOD AND LYMPH SUGAR
AFTER INJECTION
OF INSULIN
E: 1·0 UNIT INSULIN PER. KILO.
100
80
60
40
LYMPH
PLASMA
E
MIN. 60 120 180 240 300

FIG. 4.

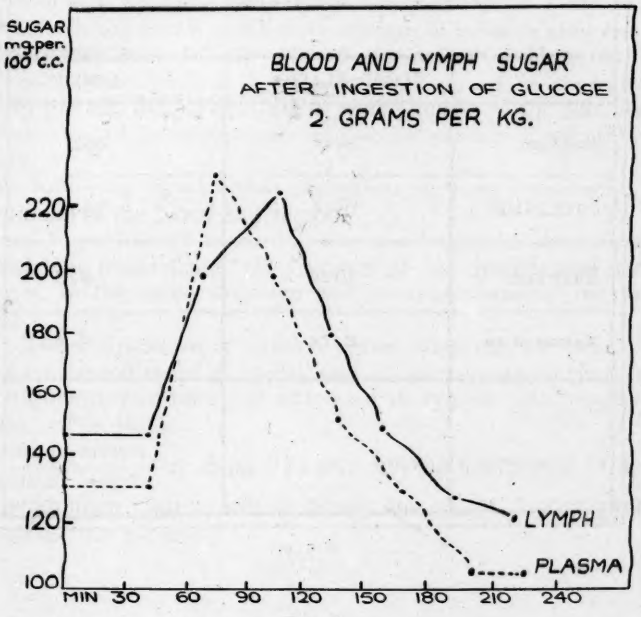

SUGAR
mg.per.
100 c.c.
BLOOD AND LYMPH SUGAR
AFTER INGESTION OF GLUCOSE
2 GRAMS PER KG.
220
200
180
160
140
120
100
LYMPH
PLASMA
MIN 30 60 90 120 150 180 210 240

FIG. 5.

3. *Administration of sugar.*—Following the administration of sugar by mouth or intravenously, there is a rapid rise followed by a fall in the plasma sugar. The following figure from Heim *et al.* (1935) shows the variations in plasma and lymph sugar after the ingestion of glucose by mouth.

It can be seen from Fig. 5 that the sugar enters the lymph stream rapidly as indicated by the almost parallel rise in lymph and plasma curves. The fall in lymph sugar follows closely that of the plasma—any slight discrepancy no doubt being due to a time-lag.

There can, therefore, be no doubt that regarding the diffusible non-electrolytes the concentration of these substances in the lymph intimately follows that in the plasma and the capillary membrane behaves in no way different from that of a semi-permeable membrane *in vitro.*

4. *The distribution of cations.*—The following table illustrates a comparison of the concentrations of certain cations in blood plasma and lymph, or for that matter any interstitial fluid such as ascitic fluid. It is seen from Fig. 6 that there are more cations

COMPARISON OF SEVERAL OF THE CATIONS IN LYMPH AND BLOOD PLASMA

	BLOOD PLASMA (- mgs. per 100 c.	LYMPH c. water -)
Sodium	344	331
Potassium	18.3	13.2
Calcium	10.4	9.2
Magnesium	2.74	2.4

FIG. 6.

in the serum than in the lymph, thus indicating that their distribution is possibly in accord with the predictions of the Gibbs-Donnan equilibrium.

I should like to discuss in greater detail the nature of the calcium concentration in lymph and blood plasma, as this will have an important bearing when the chemistry of the aqueous humour is discussed. It has been shown by test-tube experiments that the disparity in the lymph calcium is almost certainly due to the combination of this element with protein. Dialysis and ultra-filtration experiments carried out by many workers have clearly demonstrated that a certain portion of the calcium in blood plasma cannot diffuse through a semi-permeable membrane, and that the amount of this calcium varies directly with the amount of protein. We therefore speak of calcium as being present in two forms in the blood.

1. *The undissociated or indiffusible form.*—This is the calcium adsorbed on to protein and it is sometimes called calcium proteinate.

2. *The dissociated and freely diffusible form.*—It is obvious that the concentration of the calcium, free to diffuse through a membrane, be it a collodion membrane or the wall of a capillary, will depend on the amount present of—

1. Protein.
2. Total calcium.

Arnold and Mendel (1927) made a very complete study of the variations in the serum and lymph calcium in animals after experimental alterations in their calcium metabolism. These authors produced hypocalcaemia in animals by removal of their parathyroid glands, and in contrast hypercalcaemia by the subcutaneous injection of parathormone—the active extract of parathyroid glands.

The following figure shows the effects of these experiments on the calcium of the blood and lymph.

From Figs. 7 and 8 it can be seen that following alterations in the calcium metabolism, the calcium of the lymph and serum changed in the same direction and to approximately the same degree.

4. *The distribution of anions.*—Most attention has been paid to the concentration of chlorides and all workers agree that there is a higher concentration of chlorides in lymph with respect to plasma. The ratio—

$$\frac{\text{chloride in serum}}{\text{chloride in lymph}}$$

—is about 0·95 and may be interpreted in terms of the Donnan equilibrium as being due to the higher protein content of the plasma.

The phosphate ratio of—$\frac{\text{phosphate of serum}}{\text{phosphate of lymph}}$—is also about 0·95. Analyses on sulphate are not very satisfactory, but there seems no reason to doubt that the sulphate ratio would not lie in the same direction.

5. *The distribution ratio of anions and cations.*—Of great importance in the distribution of the various ions is the product of pairs of diffusible cations and anions. It is unnecessary to burden you with any more figures so I shall simply state that all workers agree that in most cases the product of a pair of diffusible cations and anions in the lymph is equal to the product of these same pair in blood plasma. Or to take a simple example—the product of Na (sodium) and Cl (chloride) in lymph and plasma is the same, the concentrations of these ions being of course expressed in gram molecules per litre. Na and Cl are chosen as they can be analysed more accurately than the other ions.

COMPOSITION OF BLOOD SERUM AND LYMPH AFTER ALTERATIONS IN THE CALCIUM METABOLISM

TIME		CALCIUM (mg./100 c.c.)
2.30 to 3.30 p.m.	Lymph	10
3.30 p.m.	Serum	11.0
4.00 p.m.	Removal of the parathyroid glands.	
10.0 a.m. next morning.	Serum	8.7
4.00 p.m.	Serum	7.9
5.00 to 8.00 p.m.	Lymph	6.8
8.00 p.m.	Serum	6.8
8.00 to 11.0 p.m.	Lymph	6.4
11.0 p.m.	Serum	6.4

FIG. 7.

COMPOSITION OF BLOOD SERUM AND LYMPH AFTER INJECTION OF PARATHORMONE

TIME		CALCIUM (mg./100 c.c.)
4.00 to 5.30 p.m.	Lymph	10.2
5.30 p.m.	Serum	11.4
7.00 p.m.	10 c.c. parathormone subcutaneously	
7.45 a.m. next morning.	Serum	16.4
11.30 to 1.00 p.m.	Lymph	15.9
12.0 noon	Serum	17.6
1.00 to 3.00 p.m.	Lymph	16.1
3.00 p.m.	Serum	17.8

FIG. 8.

The conclusions we draw on the nature of the lymph from its chemical composition is as follows:—

1. The chemical equilibrium between plasma and lymph is exactly the same as if these two solutions were on opposite sides of a collodion or other semi-permeable membrane.

2. A simple ultrafiltration or dialysis of blood plasma through the capillary wall adequately explains the mode of formation and chemical composition of the lymph.

3. These deductions based on the chemical composition are in accord with those based on the physical equilibrium which I mentioned in my first lecture—namely, that the lymph is a dialysate of the plasma.

The chemical composition of gastric juice.—The first point of practical and theoretical importance is that the osmotic pressure of gastric juice is the same as that of blood plasma. Several observers have concluded that because the osmotic pressure of a particular fluid was approximately the same as the plasma, then

that fluid must needs be a dialysate of the plasma. This conclusion does not necessarily follow, for we find that all secretions with the possible exception of saliva are isotonic with blood. In other words, although fluids such as gastric juice, pancreatic juice, hepatic bile, aqueous humour, cerebro-spinal fluid, have each their characteristic chemical composition, the total molar concentration of the various substances of which they are composed, is the same as the blood. Gilman and Cowgill (1931-32) (1933*a*) (1933*b*) have in addition shown that when the osmotic pressure of blood was raised or lowered by the injection of hypertonic NaCl or water, corresponding changes occurred in the gastric juice, bile, pancreatic juice and lymph.

It is well known by every student that the stomach secretes free hydrochloric acid and little else appears to be generally known about the chemical composition of the gastric contents; but its chemical composition will be dealt with in the same manner as that of lymph.

1. *Protein.*—Only very small amounts of protein have been found in the gastric juice and it is found chiefly in the form of mucin.

2. *Freely diffusible non-electrolytes.*—Most observers have found far less urea in the gastric contents than in plasma, but considerable amounts of ammonia have been detected in the stomach and this substance is not found in the blood. It has been suggested that the gastric mucosa contains urease, and that as the urea diffuses through into the stomach it becomes broken down into ammonia. I have found that the sum of the urea plus ammonia in the stomach of animals—chiefly cats, and in man is less than 50 per cent. of the blood urea.

With regard to the concentration of other diffusible constituents there is no information. It has been stated that no glucose is present in gastric juice, nor is glucose absorbed from the stomach. These points will be dealt with later. There is no doubt, however, that the stomach wall does not behave like a simple, semi-permeable membrane and it follows that some more complicated mechanism than simple dialysis must be present which prevents the diffusion of such easily filterable substances as urea and sugar.

3. *The distribution of cations.*—The composition of the gastric juice varies in different parts of the stomach. In the fundus there is a very high concentration of free hydrochloric acid but with practically no sodium; in the pyloric region the secretion is almost neutral and it contains equal amounts of sodium and chloride. The sodium content of the gastric juice is therefore much less than that of the plasma. The calcium content is lower and the potassium content much higher than that in the corresponding plasma. The distribution of the cations is not altogether in accord

with the Donnan equilibrium for the cations in dialysates are only slightly lower than in the protein-rich fluid.

4. *The distribution of anions.*—The chloride makes up the major part of the ions and in pure gastric secretion the Cl content of the gastric juice is equal to the total base of the blood. It follows then, that there must be a far greater concentration of chlorides in gastric juice compared with plasma than can be explained on the Donnan equilibrium and by actual analysis this has been found to be the case. Cl would appear to be the only anion found in gastric juice with the exception of a trace of phosphates.

5. *The distribution ratio of anions and cations.*—Of importance, as well as the disparity in their respective ratio, is a comparison of the products of any pair of diffusible cations and ions in the gastric juice and the blood. The product of Na and Cl in the gastric juice *does not equal the product* of Na and Cl in the plasma, so that the distribution of Na and Cl is not in accord with the Gibbs-Donnan equilibrium.

The conclusions, on the nature of the gastric juice from its chemical composition are as follows:—

1. The chemical equilibrium between plasma and gastric juice is quite different from the equilibrium that would take place if these solutions were placed on each side of a collodion or other semi-permeable membrane.

2. Simple dialysis cannot adequately explain the formation of gastric juice. Some more complicated mechanism must be present to account for—

a. The production of free hydrochloric acid.

b. The prevention of the free diffusion of such easily filterable substances as urea and sugar.

3. The chemical findings against dialysis are in accord with those based on the physical equilibrium to which I referred in my first lecture.

The Chemical Composition of the Aqueous Humour

1. *Protein.*—There is very little protein present in the aqueous humour and it has been estimated to be about 0·02 grams as compared with 8·0 grams in plasma. The very low protein of the aqueous humour and cerebro-spinal fluid is believed to be due to the presence of a second membrane reinforcing the ciliary processes and choroid plexus respectively.

2. *Freely diffusible non-electrolytes.*—A great many analyses have been carried out on the sugar content of the aqueous and a few on the concentration of the non-protein nitrogen, urea, uric acid and creatinine. The most comprehensive study has been

carried out by Walker (1933) working in Professor Richard's laboratory, and I cannot do better than quote freely from his results. He carried out 80 experiments upon frogs, fowls, rabbits, dogs, cats, and men, in which the composition of the aqueous humour was compared with that of blood from the same animal. He found :—

a. The sugar was less in the aqueous than in blood in all experiments, except those carried out on the rabbit. In rabbits, curiously enough, in three out of five animals, the sugar in blood and aqueous was the same. This chance agreement in the sugar contents of blood and aqueous in the rabbit has misled several workers into false premises.

b. The urea of the aqueous averaged 68 per cent. of that in the blood.

c. The uric acid of the aqueous averaged 66 per cent. of that in the blood.

The deficiency of urea, sugar, and uric acid, in the aqueous humour is very apparent from Walker's figures. There can be no doubt, therefore, that the membrane in the eye, intervening between blood plasma, and the intra-ocular fluid, does not behave like a simple semi-permeable membrane. If it did, then substances like urea, uric acid, and sugar should be found in the blood and aqueous in equal concentrations for they are freely diffusible and easily filtrable both *in vivo* and *in vitro*.

In addition to the above analyses on the sugar content some interesting experiments have been carried out on the sugar of the aqueous and the blood after insulin injections. It was found by Kirby, Wiener and Estey (1932) that during the rapid fall in the blood sugar after insulin the value of the aqueous humour sugar may exceed that of the blood, thus reversing the normal relationship. This is a further proof that the membrane in the eye between blood and aqueous is no simple membrane like a collodion type employed *in vitro* or like the capillary membrane in the tissue spaces throughout the body.

3. *The distribution of cations.*—The following table—see Fig. 9—illustrates a comparison of the concentrations of certain cations in blood plasma and aqueous taken from an investigation by Tron (1928).

It will be seen that the amounts of sodium, potassium, magnesium and calcium are all lower in the aqueous humour than in the plasma, and it would appear that the principle of the Gibbs-Donnan equilibrium had been supported. Closer examination, however, reveals that this may not be so, for the disparity in potassium and calcium particularly is too great to be explained by simple dialysis. Another experiment has been carried out which makes it all the more unlikely that in the eye we are dealing with simple dialysing membrane.

COMPARISON OF THE CONCENTRATIONS OF CERTAIN CATIONS IN BLOOD PLASMA AND AQUEOUS

CATIONS	PLASMA	AQUEOUS HUMOUR
Sodium	359	338
Potassium	31	19
Calcium	11.4	6.2
Magnesium	1.6	1.05

FIG. 9.

In dealing with lymph, the calcium of the lymph was found to be lower than the serum. This was explained by the fact that some calcium was adsorbed on to the protein, the calcium proteinate remaining indiffusible. When the blood calcium was raised by parathormone then the calcium of the lymph increased approximately to the same degree, and on the other hand when the blood calcium fell after parathyroidectomy a similar fall took place in the lymph calcium. These results showed that the portion of calcium joined to protein remained constant and that artificial alterations in the serum calcium level affected the diffusible calcium only because the fluctuations in the serum and lymph calcium were the same.

Now if a study is made of the aqueous humour after these experiments which alter the calcium level throughout the body, quite a different response takes place in the eye. Thus, Merritt and Bauer (1931) found that the administration of parathormone had little or no effect on the aqueous humour calcium, although adequate proof was present that these experiments alter the diffusible fraction of the serum calcium. As in the case of the cerebrospinal fluid the calcium of the aqueous humour remains remarkably

constant despite well marked changes in the serum calcium level.

4. *The distribution of anions.*—All workers have found that there is an increased concentration of chloride in the aqueous humour. The degree of this increase will be discussed when we come to a study of the Gibbs-Donnan equilibrium. With regard to the other anions such as sulphate and phosphate, these have been found to be much lower in the aqueous humour than in plasma—findings which are not compatible with dialysis.

5. *The distribution ratio of cations and ions.*—Most workers agree that the product of Na and Cl in the aqueous humour is equal to that in the plasma, in these workers' opinion establishing definite proof of the dialysate nature of the intra-ocular fluid.

In an attempt to sum up what information has been obtained from a chemical study of lymph, gastric juice, and the aqueous humour, I have tried to place the various findings in a small table —see Fig. 10.

	LYMPH	GASTRIC JUICE	AQUEOUS HUMOUR
Protein in grams per. 100 c.c.	May be above 1.	Only a trace.	Only a trace. 0.02.
Diffusible non-electrolytes such as urea uric acid creatinine sugar	Same as in plasma. Sugar follows very closely the fluctations of the blood sugar after insulin etc.	Less than in plasma. Urea 50% of plasma urea. Sugar appears to be absent.	Less than in plasma. They average 70% of plasma concentrations. Sugar does not follow the fluctuation in the blood sugar.
Cations such as - sodium potassium calcium	Less than in plasma. Calcium fluctuates closely with the serum calcium in disturbances of calcium metabolism.	Less than in plasma.	Less than in plasma. The calcium does not fluctuate with the serum calcium.
Anions such as - chloride sulphates phosphates	More than in plasma.	Chlorides greater than in plasma. No analyses on other anions.	Chlorides greater than in plasma. Phosphates less than in plasma. Sulphates less than in plasma.
The product of Na. & Cl. in terms of mille equivalents.	Equals the product of Na. & Cl. of plasma.	Is less than the product of Na. & Cl. of plasma.	Equals the product of Na. & Cl. of plasma.

FIG. 10.

The only chemical analysis of the aqueous humour in favour of simple dialysis is the fact that most workers have found that the distribution of Na and Cl is in accord with the Gibbs-Donnan equilibrium.

In conclusion I would like to refer very briefly to some experiments I have done on the chemical composition of aqueous humour and its comparison with that of the lymph, cerebro-spinal fluid and gastric juice. (Robertson and Williams, 1939).

Thoracic lymph, gastric secretion, arterial plasma, cerebro-spinal fluid, and aqueous humour were collected from the same animal in a series of cases, before and at various intervals after the intravenous injection of a solution of 50 per cent. glucose, 25 per cent. urea, and 5 per cent. creatinine. In the case of the

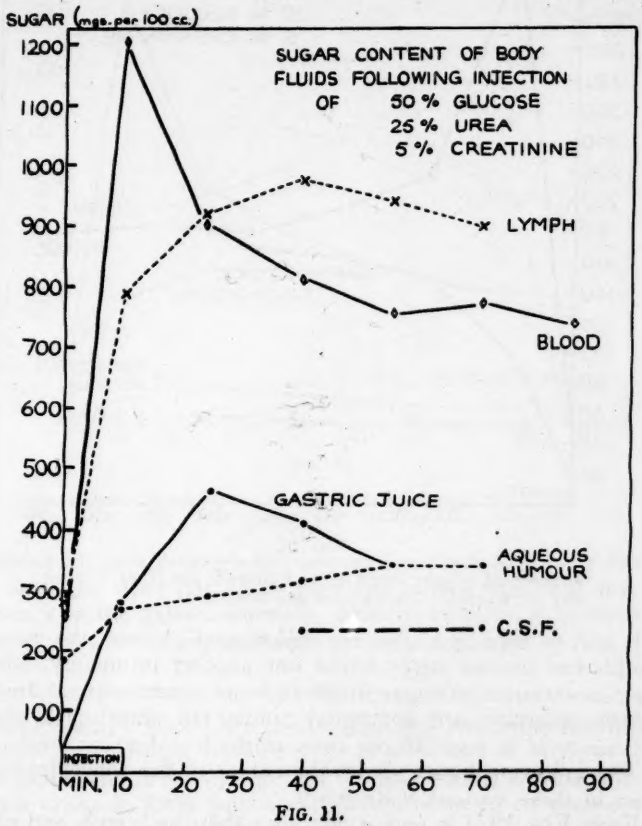


FIG. 11.

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aqueous humour, only two samples can be taken in an experiment —one from each eye, and in the case of cerebro-spinal fluid only one sample. Therefore, a series of animals was done in order to produce curves of the various constituents and the aqueous humour and cerebro-spinal fluid withdrawn at various intervals after the injection of the solution.

Fig. 11 shows the concentration of sugar in lymph, blood, aqueous humour, cerebro-spinal fluid, and gastric secretion.

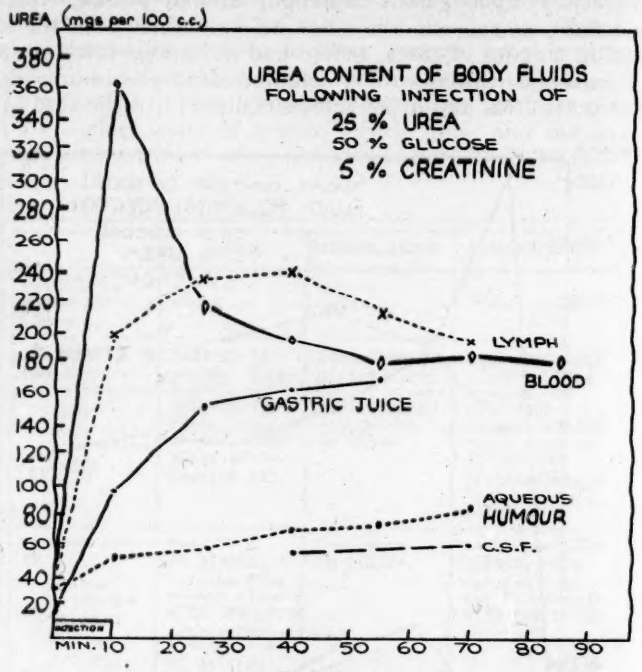

FIG. 12.

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It will be seen that after the injection of glucose, the curves of lymph and plasma sugar follow one another intimately, whereas the concentration of sugar in the aqueous, cerebro-spinal fluid and gastric secretion are somewhat similar in showing a marked deficiency of at least 40 per cent. of the blood sugar level.

The following figure shows the curves of the concentrations of urea in these various body fluids.

From Fig. 12 it is once again seen that the lymph and plasma urea follow one another intimately. As in the preceding figure, however, there is a marked disparity in the urea concentrations

of the aqueous humour, cerebro-spinal fluid and gastric secretion and the discrepancy is similar in degree in these last three fluids.

The next figure shows the curves of the concentrations of creatinine.

From Fig. 13 it will be noticed once more how similar are the curves for lymph and plasma. It is of interest to note that

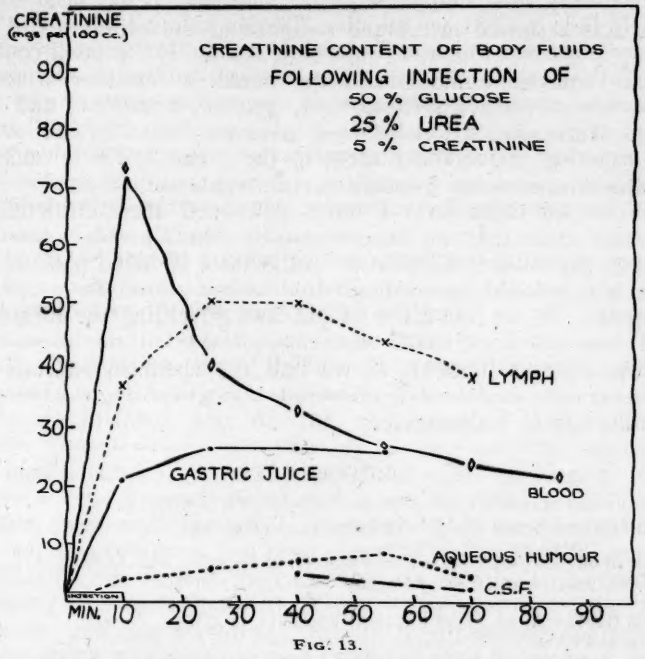

FIG. 13.

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creatinine diffuses through the stomach wall actually more easily than into the eye; but as in previous curves you will note a deficiency in the gastric secretion, aqueous humour, and cerebro-spinal fluid when compared with plasma or lymph.

Summary

I have already stated, glucose, urea, and creatinine are freely diffusible and entirely filtrable both *in vivo* and *in vitro* so that if the membrane in the eye and the choroid plexus allowed simple dialysis to occur, these substances should occur in concentrations equal to that in the plasma; but they do not. It would appear in fact that glucose, urea, and creatinine, diffuse through the

stomach wall with no less difficulty than they diffuse into the aqueous humour. In both the stomach and the eye, there is a marked deficiency in the urea, sugar, and creatinine concentrations when these are compared with the concentration of these substances in the blood. In the case of creatinine, all the experiments showed that this substance diffused into the stomach much more readily than into the aqueous humour. It has been stated that it is a second membrane re-inforcing the capillaries of the ciliary processes which is responsible for the low protein content of the aqueous humour, and the impaired filtration of freely diffusible substances such as urea, glucose, creatinine, and uric acid. This so-called re-inforced membrane behaves not unlike the secreting membrane present in the stomach, for it causes a similar concentration gradient for diffusible substances.

When all these facts I have mentioned are considered, it becomes clear that we cannot consider the aqueous humour a simple, protein-free ultrafiltrate or dialysate of blood plasma, but that it is a highly specialised fluid manufactured for a specific purpose. As we found the simple laws governing the formation and absorption of tissue fluid inapplicable to the production of the aqueous humour, so we find the chemical analysis too complex to be explained by the simple laws governing the chemical equilibrium of dialysates.

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BILATERAL MESIAL SUPERFICIAL "DEFICIENCY" OF THE SCLERA [SCLERAL PLAQUES]

BY

BASIL GRAVES*

DR. ARTHUR M. CULLER'S article in the January issue of the *Brit. Jl. Ophthal.* (pp. 44-50) with its interesting clinical and pathological report on "Scleral Plaques," induces me to submit the following article bearing on this subject. I wrote this article nearly a year ago as the first part of one more than twice the length and, meaning to abbreviate it before submitting it for publication, I put it in a drawer where it has since lain. I now submit the first part for publication unaltered, save that I have inserted, in rectangular parentheses, some comments as the outcome of Dr. Culler's informative article. I have deleted the whole of the second portion as it is only very indirectly related to the subject under discussion, being concerned with the psychology of scientific observation and evidence.

In the *Brit. Jl. Ophthal.*, October, 1937, pages 534 to 537, I wrote a short article [under the first of the two titles given above], describing some bilateral "defects" of the sclera. As the condition is bilateral and on the nasal side I had, without further consideration, and through habits indelibly ingrained in medical-student days, jumped to the conclusion that it was a developmental defect and it will be noted (p. 537) that when a patient (incidentally a very intelligent person) had told me that this condition had been observed in her eyes by herself and her friends only in the preceding six months I had, with a sweeping professional assurance that turned a deaf ear upon her evidence, and that found no difficulty in supporting dogmatism with suitable "explanations," replied that it must have been present in her since birth.† A week or two after the publication of this article I met Miss Ida Mann and she asked me whether I had considered that the condition, one affecting seemingly elderly people, could be due to a hyaline degeneration of the sclera without any structural thinning such as I had suggested might be present. [It will be noted that the idea of hyaline degeneration occurred to

* Received January 9, 1939.

† Compare the answer, in the case of Jane Throgmorton's convulsive fits (1589), given by Dr. Barrow, a celebrated physician of Cambridge, who, "perceiving the Child's Body to be in good Temper, which appeared for anything he saw to the contrary, asked if there was no Sorcery or Witchcraft suspected in the Child, to which they answered, No. Upon which he declared it was impossible it should be occasioned by any natural Cause, without any Signs appearing in the Urine: Nevertheless he desired they would send to any other skilful Man in the Town for their Satisfaction": *vide* the accounts of the accusation, trial and execution for Witchcraft of the Samwell family of Warboys, Huntingdonshire, in Thomas Wright's "Narratives of Sorcery and Magic" (1851) and Boulton's "Compleat History of Magick, Sorcery, and Witchcraft" (1715).

Dr. Culler.] This possibility had not occurred to me. Should this prove to be the case, and if further reports should confirm that the condition is confined to the nasal side of the sclera, it would be a significant matter for interesting conjecture as to whether the predisposition to such hyaline change in later life is potentially present from the embryonic period; I add this only as an afterthought and not with any intention of defending my probably erroneous suggestion that the condition is " congenital " *in toto*.

After I had written the article in the *Brit. Jl. Ophthal.* for October, 1937, I came upon a record of another case, the existence of which I had forgotten. It is reproduced in Fig. 1. (The measurements recorded are A to B and F to G, each 3·5 mm.;

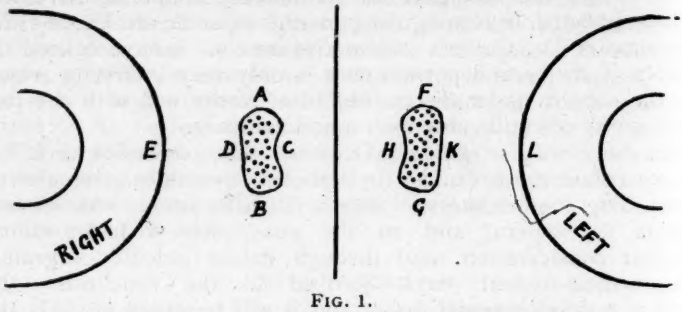

FIG. 1.

Symmetrical mesial scleral deficiencies [plaques].

C to D, *i.e.*, width at the narrowest part, 1·4 mm.; H to K, 1·6 mm.; D to E (limbus) and K to L (limbus), each 3·0 mm. The age of the patient was unfortunately not recorded but she was suffering from a recent attack of paresis of the third nerve, which I recorded as due to " ? cerebral vascular change," so she was probably elderly.) The bilateral symmetry in this case is rather striking.

In the opening words of my previous article I referred to a case which I had briefly indicated in " The Eye and its Diseases," edited by Dr. Conrad Berens, at Fig. 184, H, page 467. In a footnote on page 468 of this book I had implied that in this particular case the condition was not bilateral. In all the other cases which I had seen the condition was bilateral. Shortly after the occasion of Miss Mann's comment, this particular patient, whom I had not seen for some time, came back to me, and I looked at his sclerae and discovered that in this case, too, the condition is bilateral. Fig. 2 shows this, and differs from the figure reproduced on page 467 of Dr. Berens' book in having the two defects M and P added in the right eye. Whether the

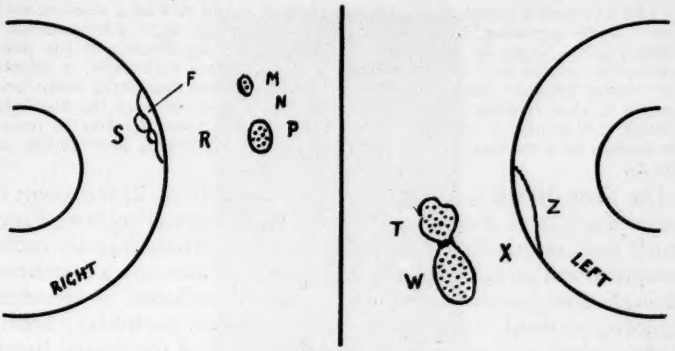

FIG. 2.

Bilateral mesial scleral deficiencies [plaques] with apparently related peripheral corneal changes in each eye.

defects M and P were present but overlooked when I first recorded this case (some years ago), or whether they have developed since, I cannot say, but reference to the figure in Dr. Berens' book will show that certain changes in the periphery of each cornea were present at the time the original records were made. It will now be seen that the corneal changes are radially opposite the areas of scleral defect and had I originally noticed that the scleral defects were bilateral I think it possible that I might, from their correlation with the corneal changes, have drawn the conclusions I am now going to suggest. The following details (except the scleral defects M and P) were recorded in my original notes of this case and when I saw the patient again after I had published my short article in the *Brit. Jl. Ophthal.* for October, 1937, I did no more than take a brief glance in which I detected the presence of M and P and confirmed that the corneal condition was substantially the same as when previously recorded.

The patient bears the name, and is the nephew, of one of the best known British ophthalmologists of the early nineteenth century. He is now 94 and is in clear possession of his mental faculties and gives many interesting reminiscences of the middle of the last century among which he recalls that a great friend of his father's stayed at their home before leaving for the Crimea, and that not long afterwards a telegram arrived announcing that this friend had been killed while second-in-command at the Charge of the Light Brigade.

The measurements of the defects (Fig. 2) and of their distance from the limbus is as follows: M (vertically), 0·9 mm.; N (space between M and P), 1·2 mm.; P (vertically), 1·8 mm.; R (distance from limbus), 3·5 mm.; T (vertically), 1·75 mm.; W (vertically), 2·5 mm.; T and W (horizontally), each 1·4 mm.; X (distance from limbus), 2·5 mm.

It would unduly prolong this article to give a full account of the corneal features and I will describe them only in so far as they seem to throw light on the scleral condition.

(An adequate account of the corneal changes would call for a separate article on " senile grooving " of the cornea which at one time interested me as affording the basis of many speculations on the significance of the almost perfectly circular and abrupt limitation of Bowman's membrane, a structure of interest because clinical evidence reveals that when considered from certain points of view it behaves clinically as might be expected from the histological entity it is known to be, but from other points of view it seems to react to influences in a manner no different from that of the stroma immediately deep to it.)

The lines drawn in the cornea at S and Z (Fig. 2) represent the limits of a type of change represented in the optical section, Fig. 3, which depicts this limitation as a line YZ (extrasectional) cutting the optical section at D, *i.e.*, about the level of Bowman's membrane. Though this particular change, casually inspected, is sometimes regarded as deep " grooving " of the corneal periphery, because of the " eroding " of the stroma to the level of the dotted line K, it is entitled to be called " grooving " only in so far as the epithelium, F, fails to rebuild the corneal surface to its normal contour-level. In this case (left eye) the optical section shows a slight surface flattening of this nature between D and E, and a similar condition is seen in an optical section of the peripheral region (F, Fig. 2) of the right eye. But in the case of the two additional small oval areas (near the letter S, Fig. 2) the eroded stroma is adequately replaced by epithelial proliferation so that, at any rate over these, the normal corneal contour is maintained. This capacity of the corneal epithelium to reproduce the normal surface contour over underlying " erosion " or atrophy of the stroma is well known, but what happens at the junction of the stroma and the basal epithelial layer to account for the fact that the epithelial replacement is full in some regions and inadequate in others is, I presume, not known. Another feature will be noticed in the optical section, Fig. 3: the normal epithelial thickness, depicted between the surface line A and Bowman's membrane B, becomes reduced (C) in the region approaching the area of main pathological change and this is obviously of interest as suggesting whether initially this whole pathological change might be one occurring in the basal epithelial cells or whether it is primarily in the superficial stroma though as yet producing no visible change in the stroma at C. If, as I shall suggest, the scleral defects are to be correlated with this " eroding " stromal change of the cornea the primary change is inferentially a stromal one since there is no basal epithelium in immediate contact with the surface of the sclera. [It is interesting to note that Dr. Culler found, in his histological sections through a scleral plaque, that " the conjunctiva and episclera were atrophic. A few globules filled with granular debris were seen lying immediately under the epithelium." (*Brit. Jl. Ophthal.*, January, 1939, p. 45.)] In Fig. 3 (which I have drawn only roughly, when without proper

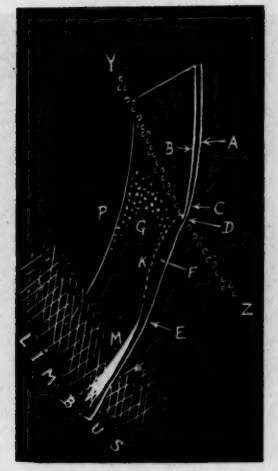

FIG. 3.

Optical section through the region z x of Fig. 2.

drawing instruments) the coarse dots above the letter G represent the arcus senilis in optical section.

The most significant feature of this case is to be found in the demarcating line YZ (Fig. 3) corresponding to the line Z in Fig. 2. It cuts the optical section about the level of the eroded edge of Bowman's membrane and by retro-illumination it consists of numerous highly refractile droplets suggestive, in their brightness, of "oily" droplets; and, unlike the slightly refractile vacuoles commonly seen in the epithelium of the cornea (which by retro-illumination show "unreversed" illumination) these droplets show "reversed" illumination.

These terms "unreversed" and "reversed" may here be explained more fully than was possible in the space available in Dr. Berens' book. I first used them in print on page 512 of the *Brit. Jl. Ophthal.* for November, 1924. The article had to be produced at short notice in compliance with the terms of a research scholarship which had terminated and my difficulty and slight delay in rendering the report lay, not in any lack of information but in selecting what to report out of a profusion of accumulated records. I therefore chose, at random, to report the interesting subject of what has since been named "cornea guttata." I had first noticed a very coarse and advanced case of this condition (Fig. 4) about 1921 or 1922 and I eventually found other but much finer examples—in which the changes at the back face of the cornea are fine isolated punctate ones (Fig. 9)—by examining the elderly inmates of an infirmary. It sounds a simple question now—as all observations are after they are confirmed—but for some time after first seeing this condition of cornea guttata I found it difficult to decide whether they were pits in, or prominences of, the back face of the cornea. At that time I had no further access to proper clinical work or I should have examined all available cases of enucleation—which in an eye hospital can doubtless amount to over 100 a

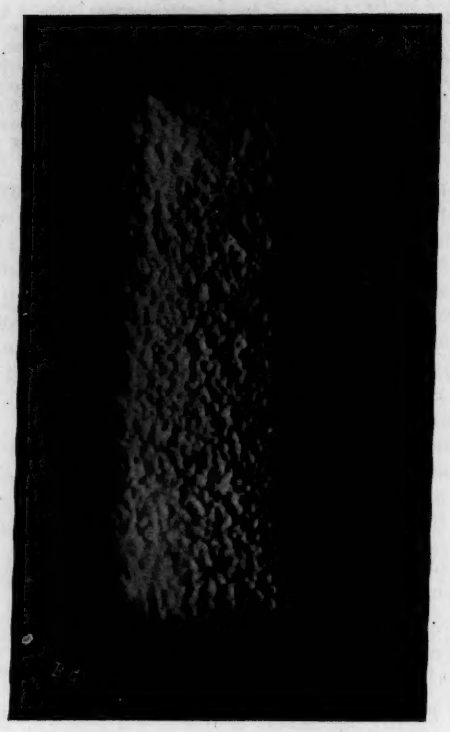

FIG. 4.

Diagrammatic representation of a very coarse and advanced case of cornea guttata by retro-illumination. Technically, this diagram is inaccurate; the individual refractile irregularities (nodules) on the east side are incorrectly portrayed as having "unreversed" instead of "reversed" illumination; and this pathological lesion should be portrayed in greater evidence in the region immediately adjoining the retro-illuminated area (indirect retro-illumination: compare the balls of K.P. indicated by P, Fig. 8) instead of, as here depicted, in the region of direct retro-illumination in front of the light-patch (compare S, Fig. 8).

year—and with probable success, since, in 1934 Dr. Everett L. Goar stated (in the *Amer. Jl. of Ophthal., vol. 27, p. 215*) that in 800 patients above the age of twenty he had found cornea guttata in about 6%. The histopathology of the condition was eventually described. Failing the possibility of getting information through histological means I had sought to interpret the optical appearances by retro-illumination of the little punctate features in cornea guttata as follows:

If ordinary vacuoles in the corneal epithelium or the lens cortex are examined by retro-illumination, it will be found that they show "unreversed" illumination, *e.g., Fig. 5, which shows vacuoles in the anterior lens cortex seen against* a small cylindrical beam of light traversing the lens-substance behind them: their light side is over against the light-beam. The same optical property of

" unreversed " illumination is revealed, faintly, in the specific condition which I have tentatively suggested should be called " superficial reticular ' vacuolation ' " (Fig. 6), and in the very fine elements of " cornea farinata " (Fig. 7) which are just within the resolvable limits at which this question can be decided. Now balls of precipitates on the back of the cornea show " reversed " illumination (Fig. 8), as do the punctate features of " cornea guttata," as indicated in the diagram, Fig. 9. A detached sphere of soft lens-matter suspended in a hernia of the vitreous in the anterior chamber after needling similarly shows " reversed " illumination. With this information collected, I attempted, in that early period, to get help to interpret these appearances of retro-illumination. Not long before that, and before I knew of the existence of the slit-lamp, I had been empirically seeking after some means of a restricted or punctate illumination of the eye (I had got assistance from various sources outside the medico-surgical profession, one in particular being a firm which then was concerned with the illumination of London theatre stages). In this, as also a little later in attempting to interpret the appearances of retro-illumination, I derived no help whatever from the orthodox text-book treatment of optics or from any medical authority who adhered to this conventional

FIG. 5.

presentation of the subject. I had taken up ophthalmology as the result of being an undergraduate student at the hospital to which Mr. Treacher Collins was ophthalmic surgeon. He retired from his hospital appointments just at the time that I eventually began to aspire to the clinical research of the type I am describing. He was essentially a man of independent thought, in no sense an imitator and above all a " craftsman " who would amuse himself making his own inductive observations and doing his own drawings of pathological conditions. He was the antithesis of the type of mind that elects to ponder on the work of other people and destructively to criticise from a theoretical elevation the work of the " practical " innovator. Most students who worked with Mr. Treacher Collins before he retired from hospital work in 1922 will probably recall the encouraging enthusiasm with which he received any new clinical suggestions or ideas, and his generous treatment of all those who made them. His mind was not closed by dogmatic systems and I think it probably not incorrect to say that he was not a great reader of the work of other people; he knew little of any foreign language. It would be interesting if anyone historically minded reviewed all Mr. Treacher Collins' published work to see how far it may bear out these personal characteristics, due allowance being made for the fact that it is impossible to gauge with historical accuracy the cross-currents of intermental thought of society meetings from the official published records in which, consciously or unconsciously, modifications and proof corrections of the papers and of the discussions can have drawn a red-herring across the trail of the significant events. It was in this spirit of inductive approach that Mr. Collins bought a slit-lamp after he had retired from hospital and would come down to learn its use of an evening at the Royal Westminster Ophthalmic Hospital where I was working for a short time. I discussed these questions of retro-illumination with him (I had already approached microscopists without any success) and I remember always his interest in the following empirical way of elucidating them which any reader may repeat for himself.

FIG. 6.
Reticular superficial " vacuolation " of the cornea.

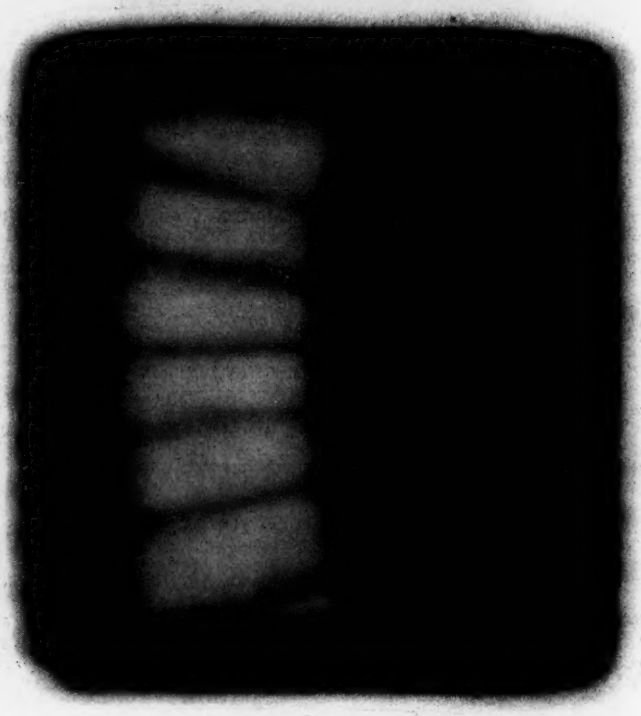

FIG. 7.
Cornea farinata.

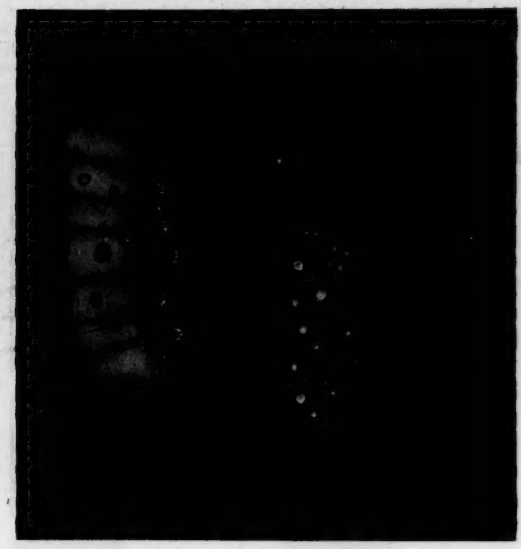

FIG. 8.

K.P. by retro-illumination and by direct illumination (and visible "flare" in the aqueous fluid).

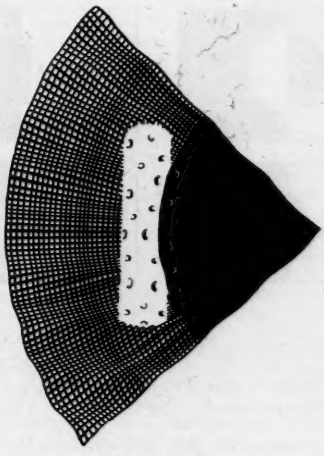

FIG. 9.

Mild Cornea Guttata (diagrammatic).

Numbers 1 to 12 used in the ensuing remarks refer to Fig. 10. Place a white sheet on a black ground, as depicted in each of the small drawings of Fig. 10. Hold, say, a 3·0 D. convex lens at some little distance in front of the boundary between black and white (1); move the lens a little eastward: the boundary moves a little westward (2). Move the 3·0 D. lens more eastward and the

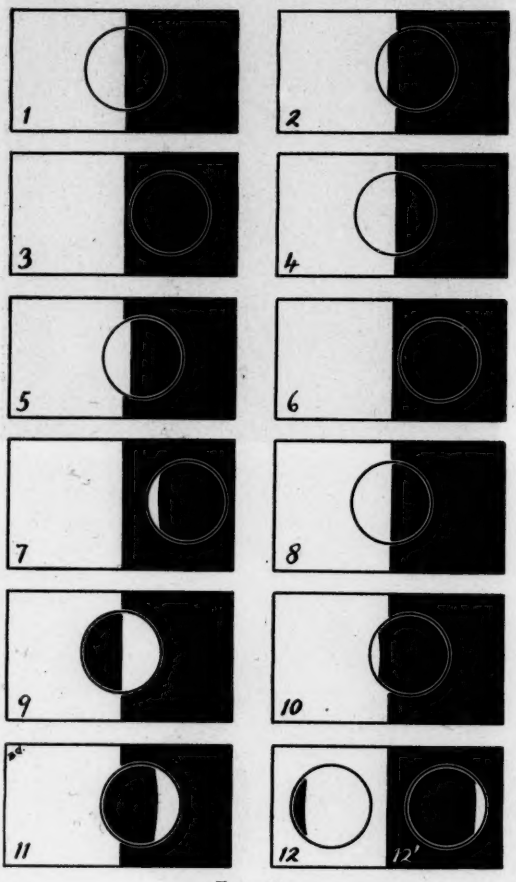

FIG. 10.

boundary is no longer seen in the lens (3). Repeat this with, say, a 3·0 D. concave lens (4, 5 and 6). Repeat 4, 5 and 6 with, say, a 16·0 D. concave lens, when the boundary is still seen in the lens (7) even though the lens is displaced considerably eastward. Now compare the diagram 7, with the picture of " unreversed illumination " of lens-vacuoles (Fig. 5, page 197). Now take a strong convex lens, say 16·0 D., hold it first quite close to, but not touching, the background as in 8, and then, keeping it opposite the boundary-line draw it further away from the background (9) and note that suddenly, at and beyond a certain distance the light and dark background as

seen in the lens become reversed. Note that if this is done with a strong concave lens no such reversal occurs, no matter what distance the lens is from the background. Now move the 16·0 D. convex lens eastward while still holding it close to the background: there is no reversal (10). Next bring it further away from the background before moving it eastward and note the "reversed" illumination (11 and 12′) and compare this with the precipitates and cornea guttata in Figs. 8 and 9, page 199.

Returning for a moment to Fig. 10, it is seen that 7 (concave lens) represents "unreversed" illumination and 12 and 12′ (convex lens held sufficiently far off) represent "reversed" illumination. But two difficulties stood in the way of inferring from this the nature of corneal and other conditions by retro-illumination. First, it was not likely that vacuoles in the corneal epithelium and the lens cortex would be biconcave; and, at any rate, in the case of the cortical lens-vacuoles, some are not infrequently big enough to disclose their convex shape in optical section, as in A, B, Fig. 11; also, histology had for years already afforded evidence of their spherical nature. Consideration of

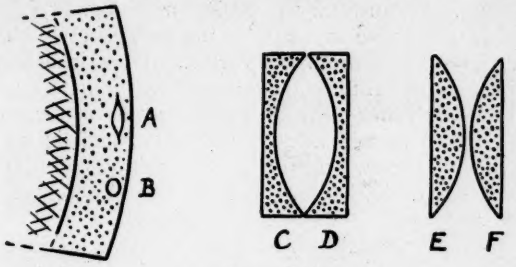

FIG. 11.

this at once suggested that their "unreversed" illumination might be explained by assuming that their refractive index, instead of being greater than that of their surrounding medium, might be less. On placing two plano-concave lenses together as one C, D (Fig. 11) so as to make a "lens" of air within glass, it was at once obvious that such a combination showed unreversed illumination as did the biconcave lens in diagram 7 of Fig. 10. But, secondly, there still remained the difficulty—as regards deciding whether the punctate features of cornea guttata, which always show reversed illumination, were depressions or elevations—that a convex glass lens shows either unreversed (diagram 10) or reversed (diagram 12′) retro-illumination according to the distance by which it is separated from the illuminated background.

Whilst still in doubt, and when not hopeful of being able to get facilities for histological evidence, an idea occurred to me one evening when I was not particularly contemplating the subject: I have referred to it on pages 527, 528 of the *Brit. Jl. Ophthal.* for November, 1924, and briefly, on pages 456 and 472 of Dr. Berens' book, "The Eye and its Diseases." It was that the difference in the axes of the Czapski microscope, owing to the convergence of its right and left halves, could be used to determine as to which way the reflecting rim of these little corneal changes was inclined and from this it could readily be decided if they were convexities or concavities. That same evening I examined a friend who, I knew, had cornea guttata, definitely ascertained for the first time that they were convexities and thereby also secured a key to settling the various difficulties in the way of understanding the question of "reversed" and "unreversed" retro-illumination in different clinical conditions and also a means of correlating these appearances with those of Fig. 10. I rang up Mr. Treacher Collins and he told me to come to his house then and explain the details to him. They are a matter of little import now, but I shall always remember the interest with which he received the information. (A story, doubtless aprocryphal, used to be current that the

late Basil Lang, when House Surgeon to the late Mr. Holmes Spicer, rang him up at 4.0 a.m. to say that a retinal detachment had gone back into place; it was not recorded how the information was received.)

It was now clear that various spheroidal or biconvex or plano-convex changes occur in or on the cornea and the lens-cortex showing " unreversed " retro-illumination when their refractive index is lower, and " reversed " illumination when their refractive index is higher, than that of the medium with which they are in contact.

The line Z, of Fig. 2 (YZ of Fig. 3) which demarcates the edge of the stromal " erosion " F (Fig. 3), and the corresponding lines shown at S, Fig. 2, reveal, as I have said above, numerous highly refractile droplets, about the level of the eroding edge of Bowman's membrane. These droplets show reversed retro-illumination, *i.e.*, they are of a material (? hyaline or fatty) which, unlike that of ordinary vacuoles in the corneal epithelium, is of a higher refractive index than the tissue in which they are imbedded. That they are highly refractile is indicated by the fact that the reversed illumination shines in them when the retro-illumination is far removed from them in a lateral direction (compare Fig. 10 (12′) in which a strong (+16) lens is used). The details of this case now suggest the correctness of the proposal [of Miss Mann and Dr. Culler] that the scleral defects may represent a hyaline change. Even so, it is feasible that the scleral defect involves an actual thinning since there is no epithelium in close contact with the sclera to make up the thickness as it does in the cornea (F, Fig. 3). The highly visible edge of these scleral defects by proximal illumination could readily be accounted for on the ground that they may be areas of active dissolution of the fibrous tissue into a refractile material like that of the corneal droplets; furthermore, the salients shown at C, Fig. 2, p. 535, of the *Brit. Jl. Ophthal.* of October, 1937, and at T in Fig. 2 in this present article, are in keeping with a possible solvent erosion by lateral spread. This Fig. 2 is also suggestive of the possibility that separate foci of the condition might spread and unite. [It will be noted that the scleral plaque in one of Dr. Culler's cases appeared two-lobed.] This condition does not seem to spread to the deep layers of the sclera but is apparently confined to the superficial part as in the cornea. [Dr. Culler's histological report indicates that the condition can involve the sclera to a considerable depth, see Fig. 3, in his article facing p. 47, *Brit. Jl. Ophthal.*, January, 1939.]

Some years ago this patient had, in the left cornea, a little down and in from the centre, a condition which I have not seen previously. A small elevation protruded, like a raspberry, about 2/3rds of a millimetre in diameter from the surface (Fig. 12). Around its site were a number of grotesquely shaped little white plaques at the level of Bowman's membrane. He complained of irritability and I asked him to return next day when I intended

to carbolise the small proturberance. When he came back next day it had gone and the epithelium at the site revealed a little defect of the surface suggesting that a sessile stump by which this proturberance might have been attached had broken off. The white plaques, unchanged, have been present ever since. [The term " plaques " as used here should not be taken to imply that the features of Fig. 12 had any refractile properties resembling the changes described under Figs. 1, 2 and 3 in this article which, optically, are very different.]

[Dr. Culler's article in the *Brit. Jl. Ophthal.* for January, 1939, affords conclusive and interesting evidence on the histo-pathology of this lesion of the sclera.] The case which I have just described, revealing related corneal changes, affords evidence which could be used as the jumping off point of various conjectures. In no science can we initially know what is important and what is unimportant. Imagine, hypothetically, the exaggerated supposition that an authority on histopathology should insist that the only avenue along which sound advance can take place in ophthalmology is through the channels of the laboratory examination of dead eyes. The mesial scleral lesion here referred to would then

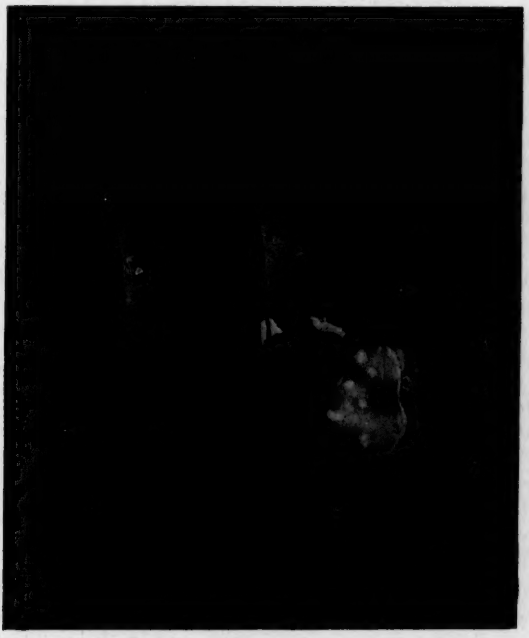

FIG. 12.

not have been recorded owing to the mere accident that it is customary to bisect dead eyes vertically and not horizontally. Correspondingly, clinical evidence alone could not suffice to clarify this condition. The whole history of medicine and surgery reveals the desirability of permitting various observational and inferential avenues of approach to its never-ceasing potential problems.

[Two or three weeks ago (January, 1939), and shortly after submitting this article for publication, I have come upon another case in a man aged 66 years. The mesial plaques are very noticeable (being extra dark) in ordinary daylight, but they are not very evident when a small beam of light is focussed on to them; and their edges do not then show up sharply in the manner described in my article for October, 1937. The left plaque (Fig. 13) measures 4·7 mm. vertically by 2·5 mm. horizontally and is 2·2 mm. from the limbus. A vessel

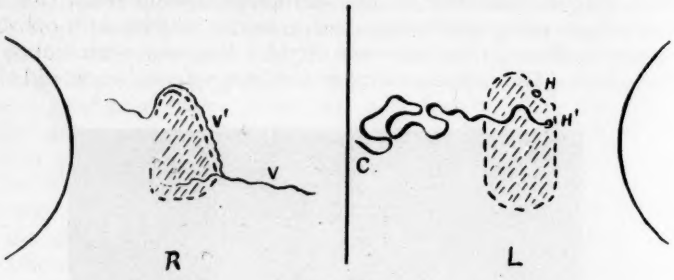

FIG. 13.

Mesial Plaques.—In this figure the diameter of the limbus has been drawn incorrectly, rather too small in proportion to the size of the plaques.

runs in the overlying conjuctival tissue from the region of the inner canthus C and enters a perforating hole, H^1, at the edge of the plaque. Above this, at the edge of the plaque, there appears to be another perforating hole, H, containing no vessel. The right plaque is triangular, though its demarcation towards the corneal side is ill-defined. It measures vertically 3·7 mm. by 2·5 mm. at its broad base, and is 2·6 mm. from the limbus. A conjunctival vessel V, after sending off a small branch which crosses the lower part of the plaque, continues on a course (V^1) which follows the contour of the plaque for some distance. There is a strong suspicion (I cannot be certain owing to the relative faintness and to the presence of pingueculae) of *a smaller dark area in each eye on the temporal side, slightly below the mid-horizontal level. In each case the distance separating these possible lateral plaques from the limbus is greater than is the case with the mesial plaques.* In the left eye the distance is 4·7 mm. and in the right eye 4·3 mm. There are no such signs in relation to the superior and inferior rectus insertions. This is the only instance in which I have seen lateral plaques.]

THE SIGNIFICANCE OF ERRORS OF REFRACTION IN CHRONIC BLEPHARITIS OF CHILDREN*

BY

E. J. SOMERSET

LONDON

THE purpose of this paper is to enquire into the significance of refractive errors as an aetiological factor in children suffering from chronic blepharitis or blepharo-conjunctivitis. Permission was obtained from the London County Council to use the ample material at White Oak Hospital, Swanley, Kent, a hospital devoted to the treatment of chronic eye diseases of children. The patients come from all parts of the metropolis and are typical of a large urban population. All the children have been referred to Swanley from hospitals and clinics in London and elsewhere after undergoing treatment generally for a long period of time. Thus they are cases which have not responded to out-patient treatment. In many instances correct glasses had been prescribed at the hospital or clinic without materially affecting the course of the disease.

In 1894 Ernest Clarke[1] investigated one hundred cases of blepharitis whose average age was seventeen years and included forty-four school children. Atropine was used for all cases under twenty and homatropine and cocaine for the remainder. Of the two hundred eyes examined his findings were as follows:

Hypermetropia	64
Hypermetropic astigmatism ...	96
Mixed astigmatism	8
Myopia	5
Myopic astigmatism	26
Emmetropia	1

He concluded that asthenopia due to ametropia was invariably present and although there was an underlying tendency to eczema or struma, the important factor in treatment was the ordering of glasses to correct the ametropia which he defined as:—

Astigmatism of more than 0·25 D., myopia and hypermetropia of more than 1·0 D.

There are few today who would agree that the normal refraction of the atropinized eye of a child is +1·0 D. It has been shown[2]

* Investigation carried out whilst holding the Royal Eye Hospital Scholarship for 1937.

that the refraction of the new-born baby is about +4·0D (atropine); as the child grows older the hypermetropia diminishes. Sorsby[3] has shown in a series of 672 unselected children at council infant schools that for children between the ages of 4 and 8 years the most common findings were from +1·50 to +3·50 D. (atropine) of hypermetropia. The maximum incidence was at +2·50 D.

A large series of 2,625 unselected children is reported on in the Report of the Committee of Inquiry into Problems connected with Defective Vision in School Children.[4] The findings cannot be considered conclusive for the following reasons :—

(1) Homatropine and cocaine only were used.

(2) There were twenty different refractionists.

(3) The highest myopic axis determined the group in myopia yet the highest hypermetropic axis determined the hypermetropic group.

Sorsby's cases are more satisfactory as they were all examined under complete atropine cycloplegia and by one observer.

In J. Hamilton McIlroy's[5] results on 1,335 children from age 7 to 13 years no cycloplegic was used.

Analysis of Findings in 300 cases at White Oak Hospital

Retinoscopy, confirmed where possible by subjective tests, was performed under atropine cycloplegia achieved by instilling atropine ointment 1 per cent. for three days.

In tabulating the results, the computed refractive error (atropine) and not the neutralising lens which might have been ordered was considered and the axis of least hypermetropia or greatest myopia was used to determine into which group any particular case was to be placed; in mixed astigmatism the myopic axis was the determinant. The eye with the less hypermetropia is the determining eye. It will be seen from Table I that the groups are recorded as −0·5, +0·5, +1·5, +2·5, etc. The +0·50 group consists of cases from +0·25 to +1·0 inclusive, the −0·50 group 0 to −0·75 and the +2·50 group cases from 2·25 to 3·0, etc. The incidence of astigmatism was considered separately.

(1) *Spherical Error.*—Table I shows the incidence of refraction in 300 children between the ages of 2 and 13 years. The sexes were nearly equal there being 159 boys and 141 girls. It will be seen that the +1·50 group represents the numerically greatest and that 75 per cent. of the cases fall into the groups from +0·5 to +3·5.

Table II is computed from the figures given in the Report of the Committee into Problems connected with Defective Vision.[4] Though not strictly comparable, it is of interest to note that groups

+0·5 to +3·5 in Table I approximately correspond to group +1·0 to +4·0 in Table II. (75·4 per cent. Table I and 81·1 per cent. Table II.

TABLE I

BLEPHARITIS. Spherical error. 300 children. Age 2—13.

Refraction	No.	Per cent.	
+9·5	2	0·7	
+8·5	1	0·3	
+7·5	0	—	
+6·5	1	0·3	
+5·5	9	3·0	
+4·5	14	4·7	
+3·5	23	7·7	
+2·5	52	17·3	
+1·5	98	32·7	=75·4 per cent.
+0·5	53	17·7	
−0·5	32	10·7	
−1·5	4	1·3	
−2·5	1	0·3	
−3·5	1	0·3	
−4·5	5	1·7	
−5·5	2	0·7	
−6·5	1	0·3	
−7·5	1	0·3	
	300	100·3	

Table III shows the figures found in the blepharitis series between the ages of 4 and 8 years, and Table IV the figures published by Sorsby of a similar age group of unselected school children. These show a similar grouping of cases round the +1·50 and +2·50 groups although the peak appears at +1·50 in the blepharitis cases and at +2·5 in Table IV.

(2) *Astigmatism.*—In recording astigmatism the method used by Sorsby has been followed. 0·25 and 0·50 have been omitted and the remainder classified as three groups, 0·75 and 1·0; 1·25 to 2·0; and 2·25 and over. The eye showing the less astigmatism determines the group.

TABLE II[4]

NORMAL. Spherical error. 2,625 children. 3—13 years.

Refraction	Per cent.	
—	—	
—	—	
—	—	
+5·0	4·7	
+4·0	6·6	
+3·0	22·9	=81·1 per cent.
+2·0	30·0	
+1·0	21·6	
0	5·2	
−1·0	2·4	
—	—	
—	—	

TABLE III

BLEPHARITIS. Spherical error. 149 children. 4—8 years.

Refraction	No.	Per cent.	
+9·5	2	1·3	
+8·5	1	0·6	
+7·5	0	—	
+6·5	1	0·6	
+5·5	3	2·0	
+4·5	12	8·0	
+3·5	15	10·0	
+2·5	32	21·5	
+1·5	38	25·5	
+0·5	23	15·4	
−0·5	17	11·4	
−1·5	1	0·6	
−2·5	1	0·6	
−3·5	0	—	
−4·5	3	2·0	
−5·5	—	—	
	149	99·5	

TABLE IV

NORMAL. 672 children. Age 4—8 years (Sorsby).

Refraction	Per cent.
+8·5	0·03
+7·5	0·09
+6·5	0·3
+5·5	1·0
+4·5	3·7
+3·5	15·3
+2·5	38·0
+1·5	28·0
+0·5	9·0
−0·5	2·0
−1·5	0·7
−2·5	0·24
−3·5	0·15
−4·5	0·04
−5·5	0·02

TABLE V

ASTIGMATISM. Blepharitis cases 3—13 years. 300 children.

Astigmatism	No.	Per cent.
0·75 to 1·0 - -	23	7·7
1·25 to 2·0 - -	25	8·3
2·25 and over - -	15	5·0
Total -	63	21·0

TABLE VI

ASTIGMATISM. Blepharitis cases 4—8 years. 149 children.

Astigmatism	No.	Per cent.
0·75 to 1·0 - -	8	5·3
1·25 to 2·0 - -	17	11·4
2·25 and over - -	7	4·7
Total -	32	21·4

Table V shows the incidence of astigmatism at all ages from 3 to 13 and Table VI records it in those children between 4 and 8 years. Table VII is that recorded by Sorsby. The percentage of children with astigmatism (21 per cent. approximately) is strikingly similar (21·4 per cent. and 20 per cent. respectively).

TABLE VII

ASTIGMATISM in 672 normal children 4—8 years (Sorsby).

Astigmatism	No.	Per cent.
0·75 to 1·0 - -	72	10·7
1·25 to 2·0 - -	49	7·3
2·25 and over - -	13	2·0
Total -	134	20·0

There is, however, a suggestion that astigmatism of over 1·0 D. is more frequent in the blepharitis cases, but no definite conclusion can be drawn on this small series.

(3) ***Uniocular cases.***—There were among the 300 children 23 cases of uniocular blepharitis, and these have been divided into three groups.

(i) Equal refraction in either eye 8 cases as follows:—

$$+0{\cdot}75,\ +1{\cdot}0,\ \frac{+1{\cdot}0}{+0{\cdot}25\rightarrow},\ +2{\cdot}0,\ +2{\cdot}0,\ +2{\cdot}5,\ +3{\cdot}5,\ +5{\cdot}5.$$

(ii) Cases of dissimilar refraction but not showing a difference of more than 0·5 D. between the two eyes and not possessing more than 0·25 D. of astigmatism. 7 cases.

	Right	Left	Eye affected
1	+0·50	+0·75	L
2	$\frac{+0{\cdot}50}{+0{\cdot}25}$	+0·50	L
3	$\frac{+2{\cdot}0}{+0{\cdot}25\rightarrow}$	+2·0	L
4	+2·50	+2·0	R
5	+2·50	+2·75	L
6	+3·50	+3·0	R
7	+4·0	+4·25	L

(iii) *Dissimilar refractions 8 cases.* Five show a greater error in the eye with blepharitis and three in the more normal eye.

	Right	Left	Eye effected
1	$\frac{-0{\cdot}25}{-3{\cdot}25\rightarrow}$	$\frac{+1{\cdot}0}{+1{\cdot}50}$	R
2	$\frac{0}{+3{\cdot}50\downarrow_{110}}$	$\frac{+0{\cdot}50}{+3{\cdot}50\downarrow}$	R
3	$-4{\cdot}50$	$\frac{-2{\cdot}25}{-0{\cdot}25\downarrow}$	R
4	$+5{\cdot}50$	$+4{\cdot}50$	R
5	$+4{\cdot}0$	$\frac{+4{\cdot}50}{+4{\cdot}50}$	L
6	$\frac{0}{-3{\cdot}50\downarrow_{50}}$	$+0{\cdot}50$	L
7	$\frac{+4{\cdot}0}{+0{\cdot}50\downarrow}$	$\frac{+2{\cdot}0}{+1{\cdot}0\downarrow}$	L
8	$+11{\cdot}75$	$+9{\cdot}25$	L

Thus of the 23 cases of uniocular blepharitis 15 do not show any marked dissimilarity in the two eyes. Furthermore 14 cases show either equal refraction in either eye or the affected eye is the more normal; only 9 show blepharitis in the eye with the greater error.

Summary. From a study of the refractive errors seen in 300 children aged 2—13 years suffering from blepharitis it is concluded that:—

(1) There is no significant difference in the spherical refractive error in children suffering from blepharitis in comparison with the normal child.

(2) The incidence of astigmatism is similar in blepharitis cases and normal children.

(3) Uniocular cases do not show blepharitis more frequently in the eye with the greater ametropia.

(4) Causes other than errors of refraction must be sought for in blepharitis of children.

My thanks are due to the Royal Eye Hospital for their grant of the Royal Eye Hospital Research Scholarship for 1937, to the

Special Hospitals Division of the London County Council and to Mr. Arnold Sorsby for his help and encouragement.

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A "PIN" EYE-DROPPER

BY

N. BISHOP HARMAN

LONDON

OILY preparations of alkaloids for the treatment of eye diseases are in many cases preferable to watery solutions. Oily preparations keep better and, in some cases, they are more effective. For example, eserine in castor oil in the palliative treatment of chronic glaucoma, or homatropine in refraction work. Oily preparations are perhaps less used than they might be owing to their messiness. This arises from too much being put into the eye by using a glass

rod or dropper. The "pin" eye-dropper meets this difficulty. It is an ordinary domestic pin fixed into a suitable handle, and the whole chromium plated. If the head only of the pin be dipped into the oil it will lift a globule of the right volume, which by a touch on the mucosa of the lower lid is transferred to the eye. The dropper can be boiled. It is made by Messrs. W. Martindale, of New Cavendish Street, W.1.

A BI-CYLINDRICAL TYPE READER

BY

G. B. LOWE, D.O.(Oxon.)

BEXHILL-ON-SEA

INCREASING the height of a letter form is well known to increase legibility owing to the reading sight travelling along the top of the print. When the lower half of a line of print only is seen, the line can scarcely be read.

This reading glass constructed for me by Messrs. Rayner stretches the type vertically, and so increases legibility. The glass is useful for those with damaged macular perception, particularly for the aged and those with obstructions in the media, whether in cornea, lens, or vitreous. It consists of two plano-cylinders of six dioptres each, lying back to back on the horizontal, giving an effective power of twelve dioptres. The handle of the glass is set obliquely to allow

an easy wrist hold. The black etched line across the lower third of the glass is an additional guide for holding it properly so that the print is seen truly vertical when the black line rules along the type below the reading level. At first the two cylinders were mounted with an air space between, but in practice it was found that a solid piece of glass prevented the possibility of the cylinders getting out of alignment, and also tended to decrease weight.

Messrs. Rayner have kindly supplied me with an illustration which explains the reader in action.

ANNOTATION

Clinics for "Special" Diseases

In medicine as practised to-day in the hospital service of large centres there is a tendency to the segregation of cases of particular diseases into special clinics. For instance, clinics and specialist teams for the care of tuberculosis, venereal diseases and rheumatism have been established longer than those which have been recently set up for diabetes, fractures, thoracic and neuro-surgery and diseases of the thyroid gland. It seems that this cleavage of certain diseases and disorders from the main body of medicine and surgery may extend to certain special branches such as ophthalmology and lead to sub-divisions here.

Recently it has been suggested by some ophthalmic surgeons that the establishment of a special clinic for retinal detachment cases would bring about in this country an improvement in the results of the operative treatment for this disorder. There is little doubt that a well chosen and competent team of clinicians and laboratory research workers dealing with a collection of a large number of cases of any particular disease will produce some good results. There are a number of points for and against such clinics. It is, however, argued by some that this growing system of special clinics is injurious to the teaching of the medical student and by others that it is beneficial and time saving. The medical undergraduate is likely to be adversely affected by the subdivision of a special subject such as ophthalmology and the detraction of patients with certain ophthalmic disorders away from the clinics of the general hospitals, whereas the post-graduate would profit by receiving instruction on a larger number of cases collected at one or several centres. A balance of the good and ill effects of this move is difficult to foresee clearly at present.

It would seem that the ideal for the time being might be for all ophthalmic surgeons who undertake operations for retinal detachment in large centres to record most carefully their clinical findings, operative technique, post-operative results and follow-up of every case of this disorder under their care. A small committee could draw up a case card of a comprehensive character and these could be collected annually at a bureau and critically reviewed and reported on in a general manner without using the names of hospitals, surgeons or patients. Such a review published annually by a select and critical committee might yield as good results as the establishment of a clinic and would at least have the advantage of being more widespread. This pooling of ideas, differences in technique and comments from a number of surgeons working on retinal detachment throughout this country would at least be worth a trial for a few years.

We draw the attention of our readers to the notes at the end of his number.

ABSTRACTS

I.—CONJUNCTIVA

(1) **Thygeson, Phillips (New York).—Treatment of staphylococcic conjunctivitis with staphylococcus toxoid.** *Arch. of Ophthal.*, August, 1938.

(1) **Thygeson's** report records the results obtained in the treatment of 57 patients with staphylococcal conjunctivitis which had resisted local measures for not less than 2 months and in the majority of cases for over a year. Toxoid was given intradermally when the injections were of less than 0·5 c.c. and subcutaneously when over this amount. It was administered bi-weekly, the initial dose being 0·01 c.c. of dilution No. 2. The dose was increased by steps of 0·02 c.c. up to 0·1 c.c. and then by 0·2 c.c. to a maximum of 1 c.c. When improvement did not occur on completion of the series, injections of 0·5 c.c. were continued at intervals for at least 6 weeks. In all cases the local treatment, which had previously been ineffective, was continued. The results in the 57 patients were: 21 healed, 19 clinically improved and 17 unchanged. Recurrences occurred in 8 of 21 healed cases and in all of these, symptoms disappeared after a second course of toxoid.

F. A. W-N.

(2) **Loe, F. (U.S.A.).—Sulphanilamide treatment of trachoma.** *Amer. Med. Jl.*, October 8, 1938.

(2) This is a preliminary report on the treatment of trachoma with sulphanilamide. This drug is para-amido-benzene-sulphonamide which is also known as prontosil album.

140 patients have been treated. The dosage was varied for patients of different weights. On the basis of their body weight they were given for each pound $\frac{1}{3}$ grain, so that a ten stone man would require approximately 45 grains; as the drug is made up in tablets of $7\frac{1}{2}$ grains this would be two tablets three times a day. Expressed in grammes, for each kilogramme of body weight the dosage would be 0·044 gramme, so that a 64 kilogramme man would require approximately 3 grammes; as the drug is made up in 0·5 gramme tablets he would require two tablets three times a day.

This dosage is less than that given of the same drug for some other infective conditions of the body.

Gradle, who is an experienced trachomatologist, reported his favourable opinion of the use of the drug in Stages II and III of the disease.

The treatment must be given under hospital conditions or under the close supervision of a medical practitioner.

Toxic effects of the drug are not uncommon (Cokkinis, *Brit. Med. Jl.*, Oct. 22, 1938), consisting of headache, palpitations or slight urticarial rash. They may be reduced by rest, glucose and increased fluid intake. The drug should not be discontinued unless the symptoms become well-marked. On the occurrence of oedema, cyanosis or dyspnoea immediate cessation of the drug and the institution of blood examinations should be undertaken.

Up to the present information is lacking that sulphanilamide has any action on viruses; as we believe that trachoma is a virus disease it will be of great interest if further experience shows that it is susceptible to the drug.

A. F. MACCALLAN.

(3) **Derkač, V. (Prelog).—Experiments with a specific treatment of trachoma. (Versuch einer spezifischen Behandlung des Trachoms).** *Arch. f. Ophthal.*, Vol. CXXXVIII, p. 270.

(3) In a series of cases **Derkač** made repeated implantations of trachomatous tissue (excised from the conjunctiva of the same or another patient) under the skin of the arm with the object of curing the disease and rendering the patient immune to re-infection.

These experiments were attended with some success, the immunisation attained being most likely due to the production of specific cyto-toxins directed against the trachoma follicles and probably also, to a lesser extent, to bacteriological antibodies directed against the trachoma virus.

Positive results were obtained in children of 9 to 14 years of age, and the tissue inoculated acted best when taken from recent untreated cases (although a short course of treatment beforehand seemed to have no bad effect) and implanted into recent cases. If re-infection did occur it was amenable to the usual treatment.

THOS. SNOWBALL.

(4) **Wolff, H. (Lund).—Ulceration keratitis and vitamin A deficiency. (Kératite Ulcéreuse et Avitaminose A).** *Acta Ophthal.*, Vol. XVI, p. 323, 1938.

(4) **Wolff** describes the case of a man with recurrent marginal ulceration of the cornea, assuming at one time a grave appearance. He holds that a liver deficiency gave rise to non-absorption of vitamin A, which in turn produced the corneal lesion. Emphasis is laid upon the need of giving vitamin parenterally.

ARNOLD SORSBY.

(5) **Sjögren, H.—Kerato-conjunctivitis sicca. (Zur Kenntnis der Keratoconjunctivitis Sicca).** *Acta Ophthal.*, Vol. XVI, pp. 70 and 80, 1938.

(5) **Sjögren** studied the histological appearances of the parotid gland in a case of kerato-conjunctivitis before the diminished secretion of saliva had set in and found disorganization of the glandular parenchyma—changes similar to those seen by Lambert and Yudkin in experimental vitamin A deficiency. He also reports the ocular changes in a patient in whom the lacrimal gland was removed during the excision of an orbital tumour, and draws attention to the similarity to the ocular findings in kerato-conjunctivitis sicca.

ARNOLD SORSBY.

BOOK NOTICES

Transactions of the Ophthalmological Society of the United Kingdom. Vol. LVIII. Part II. London: J. & A. Churchill, Ltd. 1938.

Part 2 of the Transactions of the Ophthalmological Society contains the proceedings of the Oxford Ophthalmological Congress, the Midland and Irish Ophthalmological Societies and that of South Africa, together with the year's index. The volume is of about the same thickness as the first volume of the Society in 1881. The two parts of last year run to 813 pages. The larger part of this volume belongs to the Oxford Congress and contains v. Szily's "Doyne Memorial Lecture," and important papers on "Ocular Palsies" by Professor Cairns and Dr. Chavasse. These alone make the volume of great interest, and we should not omit mention of Professor Lauber's paper on "the relationship between intra-cranial and retinal blood pressure and intra-ocular tension: the treatment of tabetic optic atrophy." Shorter papers by Mr. Harrison Butler, Mr. Williamson-Noble, Mr. F. Ridley and Dr. Traquair are also of note. We hope to notice some of these in our abstract section later in the year.

The Medical Press and Circular. Centenary Number, January 25, 1939.

We offer our cordial congratulations to the *Medical Press and Circular* on its centenary and on the extremely interesting memorial number. The paper is a combination of two journals, the *Dublin Medical Press*, founded in Ireland in 1839, and the *Medical Circular*, founded in London in 1852. These two journals combined in 1866. Ophthalmologists should be interested, for the prime mover in the

foundation of the Irish part of this journal was Arthur Jacob, one of the Masters of British Ophthalmology.

The centenary number contains a short history of the journal during its hundred years existence by Dr. Rowlette, of Dublin; the paper by Sir StClair Thomson on Victorian age, medical celebrities from the cartoons in *Vanity Fair*; papers on the last hundred years of medicine, surgery and obstetrics, by Dr. Cecil Wall, Mr. Walter Spencer and Mr. A. C. Palmer respectively, and a paper by Sir Ernest Graham-Little on the history of medical education during the last hundred years. There is also an account of Dr. James Yearsley, who had much to do with founding the *Medical Circular*, a short account of the first English medical journal of 1684, and a chronological list of Medical Societies and Journals in the British Isles.

Besides these graver matters there are some sprightly medical epigrams and entertaining snippets from the past. The number reflects the greatest credit on all concerned in its production and the Editor and his assistants are much to be congratulated on the present high standing of their paper.

CORRESPONDENCE

"RETICULAR SUPERFICAL 'VACUOLATION' OF THE CORNEA."

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—In the issue of the *Brit. Jl. of Ophthal.* for March, 1937, p. 156, I gave a brief description of a certain condition under this title. I did not illustrate it. The delicacy of the condition renders it not easy to portray. As I have included a semi-diagrammatic representation of the condition on p. 198 of my article in the present issue, may I be allowed to draw separate attention to the fact as the condition is an interesting one meriting study. The drawing here reproduced is an abstraction; it is not an actual copy of a case.

I am, Sir,

Yours truly,

BASIL GRAVES.

LONDON.
January 9, 1939.

SIGURD HAGEN

OBITUARY

SIGURD HAGEN

I regret to have to record the death of Professor Sigurd Hagen at the Eye-Clinic in Oslo.

S. Hagen was born in 1885, and he succeeded Hj. Schiöz in 1922. His interests extended to all parts of ophthalmology. His researches into the post-operative development of detachment of the choroid and of the regeneration of the aqueous of the anterior chamber deserved notice as they were published in 1920 and 1921.. He has written on glaucoma, retinoscopy, transitory hypermetropia and diabetes mellitus, melanosarcoma of the choroid and other subjects. He gave one of the opening addresses at the XIIIth International Ophthalmological Congress "Etiology and not-operative-treatment of Glaucoma." In June, 1937, he read a paper for the North of England Ophthalmological Society at the visit in Oslo, and a few months later the diagnosis of his non-tractable hypernephroma with metastases was made. In spite of that he was at work till February, 1938, and on the 12th of May his sufferings were ended.

Professor Hagen was a very skilful operator, and he had obtained great experience during his work at the University Eye Clinic in Oslo and in his private practice. He was admired by his assistants, the students appreciated highly his lectures and his patients were much attached to him. He did not like publicity and was considered to be reserved, but he had a noble character and was a gentleman through all. His death is most deplorable for Norwegian ophthalmology.

J. C. HOLST

NOTES

Deaths

WE much regret to record the death on January 18 of H. H. Woollard, F.R.S., Professor of Anatomy in University College, London. He was the author of much research on the anatomy of the central nervous system and contributed a paper on congenital ophthalmia in a puppy to our tenth volume.

It is with very deep regret that we learn of the recent death of Professor Leon von Liebermann of Budapest.

Our readers are aware that correspondence in amicable terms has been proceeding in our columns between Dr. Shimkin, of Haifa, and

Prof. v. Liebermann about the operation which is called Antepositio conjunctivae fornicis, which was described by the former at the International Congress at Cairo in 1937.

"Death quits all scores" and we should like to place it on record that Dr. Shimkin, as soon as he saw the news in the local press in Palestine, asked us to omit his last letter to us altogether. Unfortunately the number was already made up when we received his letter.

Professor von Liebermann apparently found life intolerable under present conditions. He and his wife decided to end their lives and when his body was found a circular, published by the Hungarian Government, was in his clenched hand. This circular dealt with proposed limitations of the rights of Jewish professional men and academies.

O tempora! O mores!

* * * *

North of England Ophthalmological Society.

THE tour under the auspices of the North of England Ophthalmological Society will be to the United States. Members leave Southampton on April 22 and reach New York on April 29. Visits to the New York Eye and Ear Infirmary, the Presbyterian Medical Centre, the Cornell Medical Centre and "the Lighthouse" have been arranged. An excursion to the Jones Beach on Long Island and, if possible, a day trip up the Hudson river to Bear Mountain are also contemplated. On May 5 the party will leave for Philadelphia. May 7 and 8 will be spent in Washington. The return will be on May 10 from New York by the Queen Mary, arriving at Southampton on May 15. Membership of the tour is limited to thirty ophthalmic surgeons. Applications must be addressed to Messrs. Thos. Cook & Son, Ltd., 31, Fargate, Sheffield, 1. In view of the World's Fair members wishing to join the tour should inform Messrs. Thos. Cook & Son immediately.

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Ophthalmological Society of the United Kingdom Annual Congress

IMMEDIATELY preceding the Annual Congress of the Ophthalmological Society of the United Kingdom on April 20th, 1939, the following Meetings will be held at the Royal Society of Medicine, 1, Wimpole Street, London, W.1:—

International Association for the Prevention of Blindness (Address, 66, Boulevard Saint-Michel, Paris, VI) on Wednesday, April 19, at 2 p.m. The subject will be "The application of the Crédé method for the prevention of ophthalmia neonatorum in various

countries." The speakers will be Dr. Sinclair (Edinburgh); Professors Terrien (Paris), v. Szily (Munich), Maggiore (Genoa), Vasquez Barrière (Montevideo); Dr. Wilson (Cairo), Dr. Cardell (London), Dr. C. Berens (New York). General discussion.

International Organization against Trachoma (Address, 33, Welbeck Street, London, W.1) on Friday, April 21, at 4.30 p.m. The subject will be "The incidence and clinical type of trachoma met with in Europe and North and South America, that is in countries which are commonly considered to be non-trachomatous." The speakers will be Dr. Lavery (Dublin), Dr. Harry Gradle (Chicago), Mr. Arnold Sorsby (London), and Prof. Rohrschneider (Königsberg). Subsequently there will be a short discussion on the treatment of trachoma by sulphanilamide and its congeners.

Members of the Congress are invited to attend these meetings. Ophthalmologists from abroad are invited to attend all meetings of the Congress.

* * * *

Gifford Edmonds Prize in Ophthalmology

THE next award of this prize will be made in 1941. The subject chosen for essays is "The ocular manifestations of Graves' disease." Essays must be submitted before December 31, 1940. Further particulars can be obtained from the Secretary, Royal London Ophthalmic Hospital, City Road, London, E.C.1.

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Retinal detachment bureau

THE *Brit. Jl. of Ophthal.* intends to establish a bureau for the collection of case notes concerning retinal detachment. A small committee will be formed at first, a representative chosen by each of the London Eye Hospitals and certain Provincial Hospitals to draw up a standard case sheet which is appropriate and comprehensive. These will be sent to ophthalmic surgeons interested in this subject and should be returned at the end of the year. It is hoped that the Committee after a critical review of this material will publish annually in this journal a commentary on their findings.

Mr. Charles Goulden has kindly consented to be Chairman of this Committee and Mr. H. B. Stallard is to be the Secretary.

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University of Glasgow. Department of Ophthalmology

A SHORT course of lectures on SOME ASPECTS OF MEDICAL OPHTHALMOLOGY will be given on the following dates:—

Tuesday, March 7—Professor A. J. Ballantyne.
The Eye in Disorders of the Blood and Blood-forming Organs.

Tuesday March 14—Dr. I. Chesar Michaelson.
The Eye in Diseases of the Blood Vessels.

Tuesday, March 21—Dr. John Marshall.
The Eye in the Specific Infectious Diseases.

Tuesday, March 28—Dr. John Marshall.
The Eye and Vitamin Deficiency.

Tuesday, April 4—Dr. I. Chesar Michaelson.
The Eye in the Disorders of Internal Secretion.

Tuesday, April 11—Dr. A. M. Wright Thomson.
The Eye in the Disorders of Pregnancy.

Tuesday, April 18—Professor A. J. Ballantyne.
The Eye in Functional Nervous Disease.

The lectures will be given at *4.30 p.m.* in the Tennent Memorial Building, Church Street. All interested are cordially invited.

FUTURE ARRANGEMENTS

1939

March 3.—North of England Ophthalmological Society, at Liverpool.

March 10.—Section of Ophthalmology, Royal Society of Medicine. (Clinical Meeting.)

March 31.—North of England Ophthalmological Society, at Sheffield. (Joint Meeting with the Midland Ophthalmological Society.)

April 20-22.—Ophthalmological Society of the United Kingdom, Annual Congress, at the Royal Society of Medicine.

May 4-5.—Irish Ophthalmological Society, Dublin.

May 19.—Midland Ophthalmological Society, at Gloucester Royal Infirmary and Eye Institution.

June 9.—Section of Ophthalmology, Royal Society of Medicine. (Annual.)

July 6-8.—Oxford Ophthalmological Congress, at Oxford.

October 6.—Midland Ophthalmological Society, at Birmingham and Midland Eye Hospital. (Annual.)

CONTEMPORARY OPHTHALMIC LITERATURE

American Journal of Ophthalmology. *January, 1939.*

WALSH. Facial hemiatrophy.
ALLEN and BRALEY. Staphylococcus toxin.
BURIAN. The influence of the central nervous system on the pigment migration in the retina of the frog.
BETTMAN and MCNAIR. A contact-lens-telescopic system.
LAVAL. Vitamin therapy in ophthalmic practice.
BIELSCHOWSKY. Lectures on motor anomalies. V. Development and course of strabismus.
WALDMANN. Parallel study of the pathogenesis of rhinogenous optic neuritis and of serous iritis.
ERNSTING. Intra-ocular tension in electropyrexia.
ROW and CHADWICK. Causes of blindness in India.

Annales d'Oculistique. *December, 1938.*

HARTMANN, DAVID and GUILLAMAT. Neuro-surgery in certain syphilitic localizations with involvement of the optic nerves.
CHARLIN. Essential facial neuralgias.
VIANNA. A family of Daltonians.

Revue d'Oto-Neuro-Ophtalmologie. *November, 1938.*

ALFANDARY. Introduction to the study of vestibular disharmony.
FARNARIER. Local disturbances of the retinal arterial pressure.

Klinische Monatsblätter für Augenheilkunde. *December, 1938.*

VELHAGEN, JR. Indirect crossed hemianopia.
LÖHLEIN. Permanent injury of the visual pathway in high flying.
CUSTODIS. Meningioma of the falx and localised signs suspicious of Foster-Kennedy's syndrome.
TSOPELAS. The treatment of three cases of occlusion of the central retinal artery with eupaverin Merck.
WILCZEK. Abnormal vascular supply of the retina.
KOYANAGI. Why does the periphery of the retina remain uninjured in albuminuric retinitis?
FRIEMANN. Miners' nystagmus, full equal pendulum tremor with a pituitary tumour.
OHM. Remarks on Friemann's miners' nystagmus with a pituitary tumour.
LANGE. Glioma retinae with peculiar regard to its change of colour.
VOGT. Symmetrical relations of groups of tears in terminal vessels.
VOGT. Subvascular white spots in the form of white precipitates in retinal degeneration.
RUMBAUR. Rare causes of retinal detachment.
CAILLAG. Essential iris atrophy and glaucoma.

Zeitschrift für Augenheilkunde. *December, 1938.*

D. COGAN and F. COGAN. Colour fatigue in the peripheral visual field.
RINTELEN. Flap method for optical keratoplasty.
BABEL. Ocular symptoms in swineherdsman's disease.

Bollettino d'Oculistica. *November, 1938.*

ORZALESI. The retinal arterial pressure in alcohol-nicotine amblyopia.
BELLO. Morphological genesis and aetiology of the oblique facial fissure (a case of persistent malformation of the oblique fissure with concomitant asymmetry of the facial bone).
DI BARI. The accommodation of the astigmatic eye.
CIOTOLA. The significance of follicular formations of the choroid following inoculation into the vitreous of trachomatous material.
SANTONI. Primary glioma of the optic nerve.

Archivio di Ottalmologia. *September-October, 1938.*

SIMONELLI. The function of vitamin A in the mechanism of vision.
NAPOLEONI. Research on the sense of central and peripheral light in hepatic patients with or without icterus.
CORDERO. The action of *a* dinitrophenol on the eyes.

Acta Ophthalmologica Orientalia. *January, 1939.*

FEIGENBAUM and RACHMILEWITZ. The significance of retinal findings in hypertensive vascular and renal disease.
DUGGAN and CHITNIS. Ocular lesions caused by focal infection.
ZONDEK. On the question of retrogression of bitemporal hemianopsia under internal therapy.
MEYERHOF. Remarks on trachoma healing without visible scar formation.
KOUDOVAROFF. Unilateral trachoma seen with the slit-lamp.
FEIGENBAUM. Notes on unilateral trachoma and on the question of immunity in trachoma.
STERN. Vernal conjunctivitis and dryness of the air.
KIRWAN. The development of ophthalmology in Bengal.

Archivos de Oftalmologia de Buenos Aires. *November, 1938.*

ARGANARAZ. Intracapsular cataract extraction.
ADROGUE and TETTAMANTI. Papilloedema. Pathogenesis.

December, 1938.

BALADO and SORIANO. Treatment of papilloedema.
VIDAL and COURTIS. Microscopic anatomy of the optic nerve.
ARGÜELLO and TOSI. Vogt's capsular exfoliation associated with thrombosis of a temporal vein and Stahli's line.
MALBRÁN and ADROGUÉ. Monocular diplopia in strabismus.

Klinika Oczna.

ABRAMOWICZ. Methods of localization in the eye.
GALEWSKA. A case of echinococcus recognised in time and cured by X-rays.
BIERNACKA-BIESIEKIERSKA. Asymmetry of the pupils, refraction of the eye and degree of exophthalmos.
MELANOWSKI. Traumatic scleral cysts.
SOBENSKI. Slate-coloured optic nerve.
SZYMANSKI. Subconjunctival shortening of the rectus muscle.
ABRAMOWICZ. The determination of the scleral meridian defined by means of ophthalmoscopic perimetry.
REIS. The rôle of ascorbutic acid in the chemical process of the lens.
DULEWICZ. Operative methods in the treatment of trachoma.
SZYMANSKI. The principles of Smith and Pagenstecher adapted to the subconjunctival extraction of cataract.